sertraline acetate, sertraline L-lactate or sertraline L-aspartate is administered as well as other factors which will be readily apparent to a person skilled in the art, such as a physician.

Where used herein, the abbreviation "Mpa" means megaPascals and the abbreviation "Gpa" means gigaPascals.

Where used herein, the term "osmotic tablets" defines a controlled release solid dosage form powered by osmotic pressure.

For convenience and consistency, reference to "sertraline" in terms of therapeutic amounts or in release rates in the claims is to active sertraline, abbreviated herein as "mgA", i.e., the non-salt, non-hydrated free base having a molecular weight of 306.2 g/mole. Amounts in mgA can conveniently be converted to equivalent weights for sertraline acetate, which has a molecular weight of 366.3 g/mole. The molecular weight of the 1/4 hydrate form of sertraline acetate is 370.8 g/mole. The molecular weight of sertraline L-lactate is 396.3 g/mole. The molecular weight of sertraline L-aspartate is 439.3 g/mole.

The invention will now be illustrated by the following examples which are not to be taken as limiting. In general, the examples demonstrate the incidence of gastrointestinal side-effects upon oral and IV dosing of sertraline, the amelioration of these side effects by controlled release dosing, and the preparation of sustained-release dosage forms of sertraline within the scope of this invention, salts, processes for making same, and so forth.

In the examples that follow, the following definitions and tests have been employed:

1. "Q" is used to designate a quantity of sertraline either in mgA or in percent (%), as indicated. The Q is associated with a time or "pull point" at which an indicated aliquot of solution was removed for assay of sertraline, the time of removal or pull point being designated in hours as a subscript. Thus, a "Q_1" of 15% means that 15% of the sertraline dose was dissolved in 1 hour.

2. Specification of a quantity in percent (%) means percent by weight based on total weight, unless otherwise indicated.

3. "$t_{80\%}$" means the time, in hours, for 80% of sertraline dose to be released from the dosage form.

4. Release rate is defined by the following equation:
release rate = 0.8 * (dose) / $t_{80\%}$ or Q_{24}/24 if 80% of the sertraline is not released within 24 hours

5. "Surelease®" is the registered trademark of Colorcon Inc., West Point, PA for an aqueous, fully plasticized polymeric dispersion of ethylcellulose.

6. "Opadry®" is the registered trademark of Colorcon Inc., West Point, PA for a family of plasticized cellulose ethers which include hydroxypropyl methylcellulose, hydroxypropyl cellulose and methylcellulose that are supplied as powders for reconstitution in water.

7. "mgA" is an abbreviation for "milligrams of active sertraline". For example, "200 mgA" means 200 mg of active sertraline.

8. "X mgA of multiparticulate" (where X is a number) means the amount of multiparticulates containing X mgA. For example, "100 mgA of multiparticulates" means the weight of multiparticulates containing 100 mg active sertraline.

9. In Vitro Dissolution Test: The following *in vitro* test can be used to screen sustained release embodiments of this invention for *in vivo* suitability. If a particular dosage form satisfies the *in vitro* criteria or the *in vivo* criteria disclosed herein, it is within the scope of this invention.

Sustained release dosage forms of sertraline are tested in a standard USP rotating paddle apparatus as disclosed in United States Pharmacopoeia XXIII (USP) Dissolution Test Chapter 711, Apparatus 2. Paddles are rotated at 50rpm (or 100 rpm if the dosage form is multiparticulate or disintegrates quickly into multiparticulates) and the dissolution is conducted in, as the test medium, 900 mL acetate buffer (0.13M acetic acid) with 0.075M sodium chloride using potassium hydroxide to adjust pH to 4.0, at 37°C. The dissolution vessels are covered to prevent evaporation. If gelatin capsules are used, then 0.1mg/mL of the enzyme trypsin must be added to the buffer. At indicated times following test initiation (i.e. insertion of the dosage form into the apparatus), filtered aliquots (typically 2 or 10mL) from the test medium are withdrawn and analyzed for sertraline by reverse-phase high performance liquid chromatography (HPLC) or other suitable quantifiable analysis method. Dissolution results are reported as mgA sertraline dissolved versus time or percent of active sertraline dissolved versus time. Sustained release dosage

forms that meet the following criteria are within the scope of the invention: during the initial time over which 80% of drug loading is released (1) the sertraline release rate is between 1 mgA/hr and 40 mgA/hr, as defined above; and (2) the sertraline release rate cannot exceed 40 mgA/hr during any one hour period; and, (3) less than 70% of the incorporated sertraline is released during the first hour in the use environment.

For a delayed plus sustained release embodiment wherein the delay is temporal, the same test as described immediately above for pure sustained release embodiments is employed without any modification. The dosage form will release sertraline at a rate less than 1 mgA/hr for a period of up to three hours or less, corresponding to the delay period, followed by sustained sertraline release at a rate of from 1 mgA/hr to 40 mgA/hr thereafter.

A convenient test for a spatially delayed plus sustained release embodiment of the current invention is a modified version of a two part *in vitro* dissolution test, which is described in the 1995 US. Pharmacopoeia (USP 23), Section [724], Subsection "Delayed Release (Enteric-coated) Articles - General Drug Release Standard", which incorporates a 2 hr test of sertraline release in a simulated gastric fluid ("acid test"), followed by a test of drug release in a simulated intestinal fluid ("neutral test"). For tablets and capsules which do not contain multiparticulates or disintegrate rapidly into multiparticulates, stirring is effected using paddles at 50 rpm. For multiparticulates or dosage forms that disintegrate into multiparticulates, stirring is effecting using paddles at 100 rpm. If gelatin capsules are used, then 0.1 mg/mL of the enzyme trypsin must be added to the buffer. This two stage *in vitro* test is adjusted to be useful in evaluating spatially delayed plus sustained embodiments of this invention, as now described.

For pH-triggered spatially-delayed plus sustained release embodiments, the *in vitro* test is carried out as described in the USP "Enteric Test", with the requirements that dosage forms of the invention (a) release sertraline at a rate not exceeding 1 mgA/hr for at least one hour during the "acid" phase of the test (in 0.1 N HCl), and (b) release sertraline at a rate between 1 mgA/hr and 40 mgA/hr in the neutral phase of the test, provided that the dosage forms release no more than an additional 70% of the incorporated sertraline in the first hour of the neutral phase of the test. If

desired, the acid phase portion of the test can be carried out for longer than 1 hour, i.e., under even more stringent conditions and such embodiments are also within the scope of the invention. Calculation of the sertraline release rate during the neutral phase of the test is as follows. The rate is calculated by noting the time following the 1 hour delay during which an additional 80% of the dose has been released into the neutral (pH 6.8) medium, then carrying out a division in which the numerator is 80% of the dose in mgA, and the denominator is the time at which an additional 80% of the dose is released into the neutral medium minus 1 hour (or other time period if the acid phase is longer than 1 hour). The acid portion of the test is carried out in 750 ml 0.1N HCl, for 1 hr. After 1 hr, 250 ml 0.2M tribasic sodium phosphate, containing 10 gm polysorbate-80, is added to the acid medium (containing the dosage form), and the pH is adjusted to pH 6.8, using either 2M hydrochloric acid or 2M sodium hydroxide. The solubility of sertraline is low in phosphate buffer (pH 6.8). Thus polysorbate-80 (1% w/v) is added to the neutral (pH 6.8) phosphate medium to increase the sertraline solubility to provide "sink conditions" for dissolution.

For enzyme-triggered spatially-delayed plus sustained release embodiments described in this disclosure, release of sertraline is "triggered" by the presence of pancreatic lipase, esterase, or protease in the small intestine. For *in vitro* evaluation of lipase-triggered delayed plus sustained release dosage forms, 5 mg/ml porcine pancreatic lipase (Sigma Chem., St. Louis, MO) is included in the dissolution medium for the second neutral stage of the dissolution test. For esterase- or protease-triggered delayed release systems, appropriate esterases or proteases (e.g. pancreatic esterase, trypsin, chymotrypsin, elastase) are included in the second stage of the *in vitro* test. Thus the test is conducted in the same manner as for pH-triggered spatially delayed forms, but the neutral phase is conducted in the presence of an enzyme suitable for triggering the onset of sustained release. If the esterase, protease, or lipase is denatured by polysorbate-80, then the first hour of the "neutral" phase is carried out in the presence of enzyme and absence of polysorbate-80. After one hour in the "neutral" phase, 10g of polysorbate-80 is added.

Example 1

This example demonstrates that sustained release dosing of sertraline (200 mg dose as sixteen 12.5 mg doses given at time zero and every hour for 15 hr) results in decreased side effect severity, relative to a single 200 mg bolus dose.

In a double-blind, randomized, placebo-controlled parallel group study, healthy male human subjects were divided into three groups. Group A, referred to as the "bolus dosing group", received a single 200 mg sertraline dose as two 100 mg sertraline immediate release tablets (ZOLOFT®). The tablets were administered with 50 ml water. The bolus dosing group also received a 50 ml placebo solution every hour for 15 hours. The placebo solution contained lactose, menthol, and polyvinylpyrrolidone to mimic the appearance and mouth feel of the sertraline solution, to assure blinding. Group B, referred to as the "divided dosing group", received the same total dose, administered as a solution of 12.5 mg sertraline solution in 50 ml of water at the rate of one 12.5 mg dose each hour for 15 hours. Group B also received two placebo tablets at the first dosing time. Group C, referred to as the "placebo group", received placebo tablets and placebo solutions at the appropriate corresponding time points. All subjects were dosed after an overnight fast.

Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,12,13,14,15, 16, 18, 20, 22, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 240 hr post-dosing. Plasma sertraline concentrations were determined using capillary gas chromatography. Total systemic exposure to sertraline was determined by measuring the area under the plasma sertraline concentration vs. time curve (AUC) for each subject in a given group, and then by calculating a mean AUC for the group. C_{max} is the maximum observed plasma sertraline concentration achieved in a subject. T_{max} is the time at which C_{max} is achieved. Plasma pharmacokinetic data for this example are presented in Table 1-1.

Prior to dosing and to each blood sampling time, each subject filled out a questionnaire, which consisted of a series of "Visual Analogue Scales" in which the subject was required to rate, on a scale of 0-10, the severity of certain potential side

effects. The subjects were instructed that "0" indicated an absent effect and "10" indicated the worst possible effect.

A total of 45 subjects completed this study: 15 each in Groups A, B, and C. For eight side effects evaluated at 30 time points, a total of 10,800 individual visual-analogue-scale evaluations were obtained.

Table 1-1 demonstrates that the total systemic sertraline exposure of the two dosing groups, Groups A and B, as reflected in the AUC, was similar. For the divided dosing group, C_{max} was lower and T_{max} was longer, as expected, because the dosing took place over 15 hr, rather than a single bolus dose. Three subjects in the 200 mg bolus dose group had emesis at 4.25, 11.2, and 7.6 hr. Since the emesis occurred after substantial plasma concentrations were achieved in all three subjects and after T_{max} in two, the data from these subjects were not treated differently than the data from other subjects. Subjects on the 15 hr divided dose regimen experienced no emetic episodes. Thus the 15 hr divided dose regimen exhibited a decreased incidence of emesis, relative to the bolus dose regimen.

Analysis of side effect visual-analogue-scale data was carried out as follows. For a particular side effect (e.g., abdominal pain) in a particular subject, visual-analogue-scale scores over the 24 hr post-dose period were summed to give a "cumulative score". "Cumulative scores" for all members of a treatment group were summed, and divided by the number of subjects in the group, to give a Mean Cumulative Score. The scale of this Mean Cumulative Score does not correspond to the original 0-10 scale, since it reflects the summation of all non-zero scores over the entire evaluation period. Table 1-2 presents Mean Cumulative Scores for a series of gastrointestinal side effects: abdominal pain, nausea, urgency to defecate, regurgitation, diarrhea, and abdominal cramping. The non-gastrointestinal side effects dizziness and tremor were also evaluated.

Table 1-2 demonstrates that the overall severity of sertraline-induced side effects was lower for the 15 hr divided dose treatment.

Table 1-1

Sertraline Pharmacokinetics For a
200 mg Dose given as a Single Dose, or as Sixteen 12.5 mg doses
every Hour for 15 Hours (mean values).

TREATMENT	C_{max} (ng/ml)	T_{max} (hr)	$AUC_{O\text{-}last}$ (ng.hr/ml)
200 mg single dose (Group A)	74	6	1646
12.5 mg per hr for 15 hr (Group B)	32	16	1227

Table 1-2

Mean Cumulative Visual Analog Score Data for Various
Side Effects, averaged over all 15 subjects in each group.
See text for explanation of "mean cumulative score."

MEAN CUMULATIVE SCORE

SIDE EFFECT	GROUP A (Bolus Dose)	GROUP B (16 Divided Doses)	GROUP C (Placebo)
Abdominal Pain	2.7	0.1	1.7
Nausea	17.5	2.6	1.2
Urgency to Defecate	3.1	0.5	0.6
Regurgitation	4.0	0.3	0.3
Abdominal Cramping	3.1	0.1	0.9
Diarrhea	3.9	0.2	0.2
Dizziness	13.8	0.5	6.8
Tremor	7.9	1.7	0.5

Example 1 further demonstrates that (1) side effects may be ameliorated by controlling the rate at which sertraline is released into the gastrointestinal tract, (2) delivery at a rate of 200 mg/15 hr = 13.3 mg/hr results in a decrease in gastrointestinal and systemic side effects compared to bolus dosing with the divided-dose side effect severity at or near placebo levels (Table 1-2), and (3) sustained

release dosage forms which contain less than 200 mg sertraline also have an advantageous side effect profile. In the course of carrying out the first half of the 200 mg/15 hr divided dose study of this example, eight 12.5 mg doses were delivered over 7 hr, with low observed side effect intensity (total dose 100 mg). Likewise, during the first quarter of the 200 mg/15 hr divided dose study of this Example, four 12.5 mg doses were delivered over 3 hr, with low observed side effect intensity (total dose 50 mg).

From another perspective, side effects (particularly tremor and dizziness, which are systemically mediated, and not mediated by direct contact of sertraline with the gastrointestinal tract) may be ameliorated by controlling the maximum sertraline concentration in the systemic circulation after oral dosing. In this Example, the 16 x 12.5 mg divided dose gave a C_{max} of 32 ng/ml, with very low side effect severity. On the other hand, the 200 mg bolus dose gave a C_{max} of 74 ng/ml, and exhibited significant side effects.

Example 2

This example demonstrates that sustained release dosing of sertraline (200 mg dose as eight 25 mg doses given at time zero and every hour for 7 hr) results in decreased side effect severity, relative to a single 200 mg bolus dose.

In a double-blind, randomized, placebo-controlled parallel group study, healthy male human subjects were divided into three groups. Group A (n=14) received a single 200 mg sertraline dose as two 100 mg sertraline immediate release tablets (ZOLOFT®) ("bolus dosing" group). The tablets were administered with 50 ml water. Group A also received a 50 ml placebo solution every hr for 7 hr. The placebo solution contained lactose, and menthol. Group B (n=16) received the same total dose, administered as a 25 mg sertraline solution (in 50 ml) at the rate of one 25 mg dose each hr for 7 hr ("divided dosing" group). Group B also received two placebo tablets at the first dosing time. Group C (n=15) received placebo tablets and placebo solutions at the appropriate time points. All subjects were dosed after an overnight fast.

Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 13, 15, 17, 24, 48, 72, 96, 120, and 144 hr post dosing. Plasma sertraline

concentrations, C_{max}, T_{max}, and AUC were also determined in the same manner. Plasma pharmacokinetic data for this example are presented in Table 2-1.

Prior to dosing and each blood sampling time, each subject filled out a questionnaire, which consisted of a series of "Visual Analogue Scales" as described in Example 1. A total of 45 subjects completed this study. For three side effects evaluated at 30 time points, a total of 4,500 individual visual-analogue-scale evaluations were obtained.

Table 2-1 demonstrates that the total systemic sertraline exposure of the two dosing groups, reflected in the AUC, was similar. For the divided dosing group, C_{max} was lower and T_{max} was longer, as expected because the dosing took place over 7 hr, rather than in a single bolus dose. Four subjects in the 200 mg bolus dose group had emesis at 2.6, 2.8, 2.8, and 3.8 hr. The pharmacokinetic data from these four subjects were not included in the averages presented in Table 2-1. One subject on the 7 hr divided dose regimen had emesis at 12.6 hr. Since this occurred 3.5 hr after T_{max} for this individual, his data were included in the average analysis for the divided dosing group. The observation of 4 and 1 emetic events for the bolus dose and divided dose groups, respectively, indicates that 7 hr divided dosing gave a lower incidence of emesis, while providing a therapeutic sertraline dose as evidenced by pharmacokinetic AUC.

Analysis of side effect visual-analogue-scale data was carried out as described in Example 1. Table 2-2 demonstrates that the overall severity of sertraline-induced side effects was lower for the 8 divided dose treatments.

Thus side effects may be ameliorated by controlling the rate at which the sertraline is released into the gastrointestinal tract. Example 2 thus demonstrates that delivery at a rate of 200mg/7hr = 28.6 mg/hr (or slower) results in a decrease in side effect severity (Table 2-2).

Example 2 also demonstrates that sustained release dosage forms which contain less than 200 mg sertraline have an advantageous side effect profile. In the course of carrying out the first half of the example, four 25 mg doses were delivered over 3 hr, with low observed side effect intensity (total dose 100 mg).

As for Example 1, this example also demonstrates that side effects, particularly tremor and dizziness, may be ameliorated by controlling the maximum sertraline concentration in the systemic circulation after oral dosing. In this Example,

the 8 x 25 mg divided dose regimen gave a C_{max} of 46 ng/ml, while the 200 mg bolus dose gave a C_{max} of 75 ng/ml. The 8 x 25 mg divided dose regimen exhibited lower side-effect severity than the bolus dose regimen.

Table 2-1

Sertraline Pharmacokinetics For A
200 mg Dose given as a Single Dose, or as Eight 25 mg doses every Hour for 7 Hours (mean values).

TREATMENT	C_{max} (ng/ml)	T_{max} (hr)	$AUC_{0\text{-last}}$ (ng.hr/ml)
200 mg single dose	75	5.4	1744
25 mg per hr for 7 hr	46	10.4	1439

Table 2-2

Mean Cumulative Visual Analog Score Data for Various Side Effects, averaged over all 15 subjects in each group. See test for explanation of "mean cumulative score".

MEAN CUMULATIVE SCORE

SIDE EFFECTS	GROUP A (Bolus Dose)	GROUP B (8 Divided Doses)	GROUP C (Placebo)
Regurgitation	3.9	0.1	0.1
Dizziness	10.4	4.8	2.1
Tremor	8.9	2.7	0.3

Example 3

This example demonstrates that the absorption of sertraline differs when sertraline is dosed directly to various portions of the gastrointestinal tract. Dosage forms which deliver most of their sertraline load before reaching the transverse or descending colon give higher systemic sertraline exposure than dosage forms which deliver a significant portion of their sertraline load in the transverse or descending colon.

Two groups of 6 volunteers (Groups A and B) each were dosed with 200 mg sertraline or placebo by different four-way crossover regimens. Dosing was via (1) oral tablets, or (2) infusion of a solution through a nasoenteric tube into the stomach, duodenum, or ileocecal region of the small intestine, or (3) infusion into the transverse colon via anal intubation.

On four different occasions, Group A received (1) oral sertraline immediate release tablets plus placebo solution infused into the stomach, or (2) oral placebo tablets plus sertraline solution infused into the stomach, or (3) oral placebo tablets plus sertraline infused into the small intestine at the ileocecal junction, or (4) oral placebo tablets plus placebo solution infused into the small intestine at the ileocecal junction. On four different occasions, Group B received (1) oral sertraline immediate release tablets plus placebo solution infused into the duodenum, or (2) oral placebo tablets plus sertraline solution infused into the duodenum, or (3) oral placebo tablets plus sertraline infused into the transverse colon, or (4) oral placebo tablets plus placebo solution infused into the transverse colon.

The oral sertraline dose was administered as two 100 mg tablets. The infusions were administered as a 2 mg/ml solution at a rate of 20 ml/min for 5 min.

Blood samples were withdrawn prior to dosing, and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 192 and 240 hr post-dosing. Plasma sertraline concentrations, C_{max}, T_{max}, and AUC were also determined as in Example 1. Plasma pharmacokinetic data for this example are presented in Table 3-1.

Table 3-1 presents the observed average C_{max}, T_{max}, and AUC for the various dosing regimens. Infusion into the stomach and duodenal regions gave an AUC (total systemic exposure) which was 79% and 110% of the AUC observed after dosing with oral tablets. Thus absorption from these regions of the gastrointestinal tract (in addition to more distal regions since the dosed material moved distally with time) was similar to that from oral tablets. Infusion into the ileocecal region of the small intestine resulted in an AUC which was 62% of that observed after dosing oral tablets. Thus the ileocecal region (in addition to more distal regions) has limited capacity for absorption of sertraline. Infusion into the transverse colon resulted in an AUC which was 16% of that observed after dosing oral tablets. Thus the transverse (and more distal descending) colon has a more limited capacity for absorption of sertraline.

Table 3-1

Pharmacokinetics of 200mg sertraline delivered to various portions of the gastrointestinal tract.

GROUP A			
Dosing Route	C_{MAX} (ng/ml)	T_{MAX} (hr)	AUC_{0-LAST} (ng · hr/ml)
Oral Tablet	39.9	7.0	1174.5
Stomach Infusion	35.6	7.0	923.1
Ileocecal Infusion	27.3	5.0	727.1
GROUP B			
Dosing Route	C_{MAX} (ng/ml)	T_{MAX} (hr)	AUC_{0-LAST} (ng · hr/ml)
Oral Tablet	44.7	6.7	1153.4
Duodenal Infusion	48.8	3.7	1270.3
Colonic Infusion	10.9	4.4	179.4

Example 4

This example illustrates making sustained release sertraline hydrophilic matrix tablets which release sertraline at different rates depending on their composition, size and shape. The processing comprised (1) blending all components, as designated in Tables 4-1, 4-2 and 4-3, except for magnesium stearate; (2) screening and reblending the same components; (3) adding and blending magnesium stearate; and (4) compressing the final blend into tablets.

In batch sizes of 200 - 350 grams, sertraline hydrochloride was blended in a suitable jar with all other components except magnesium stearate for 15 minutes using a Turbula shaker system (Basel, Switzerland). Next, the blend was passed through a 20 mesh screen and shaken again for 15 minutes. Then, magnesium stearate was added and the blend was shaken for 2 minutes. Using a conventional tabletting press (Manesty F-Press, Manesty Machines, Liverpool, England), the final blend was compressed into tablets using either 1/4 inch by 3/4 inch capsular tooling punches for Examples 4A-4M, 13/32 inch standard round concave (SRC) punches

for Examples 4N and 4O, 1/4 inch by 1/2 inch capsular tooling punches for Examples 4P-4X, or 1/4 inch by 9/16 inch capsular tooling punches for Examples 4Y-4AD. A summary of the compositions manufactured by direct compression of the formulation blend at 200mgA sertraline per tablet is shown in Table 4-1 for Examples 4A through 4O, at 100mgA sertraline per tablet is shown in Table 4-2 for Examples 4P through 4X, and at 50mgA sertraline per tablet is shown in Table 4-3 for Examples 4Y through 4AD, respectively.

Table 4-1

Sustained Release Hydrophilic Matrix Tablet Compositions Manufactured by Direct Compression on the F-Press with Dosage Strength of 200mgA/tablet.

Example	% Sertraline Compound*	% HPMC K100LV[1]	% HPMC K4M[2]	% Lactose	% DCP[3]	% MgSt[4]	Tablet Weight (mg)
4A	29.8	24.9	5.0	-	39.3	1.0	750
4B	29.8	34.9	5.0	-	29.3	1.0	750
4C	29.8	41.6	8.2	-	19.4	1.0	750
4D	39.8	24.9	5.0	-	29.3	1.0	562
4E	29.8	24.9	5.0	39.3	-	1.0	750
4F	29.8	34.9	5.0	29.3	-	1.0	750
4G	29.8	41.6	8.2	19.4	-	1.0	750
4H	39.8	24.9	5.0	29.3	-	1.0	562
4I	30.0	20.0	10.0	38.0	-	2.0	750
4J	30.0	15.0	15.0	38.0	-	2.0	750
4K	30.0	50.0	10.0	8.0	-	2.0	750
4L	30.0	33.3	16.7	18.0	-	2.0	750
4M	30.0	25.0	25.0	18.0	-	2.0	750
4N	39.8	24.9	5.0	-	29.3	1.0	562
4O	39.8	24.9	5.0	29.3	-	1.0	562

[1] HPMC means hydroxypropyl methylcellulose, Methocel K100LV (Dow Chemical, Midland, MI)

[2] HPMC means hydroxypropyl methylcellulose, Methocel K4M (Dow Chemical, Midland, MI)

[3] DCP means dibasic calcium phosphate dihydrate, Emcompress (Edward Mendell Co., Surrey, UK)

[4] MgSt means magnesium stearate

* % sertraline compound reflects quantity of sertraline salt needed to achieve 200 mgA.

Table 4-2

Sustained Release Hydrophilic Matrix Tablet Compositions Manufactured by Direct Compression on the F-Press with Dosage Strength of 100mgA/tablet.

Example	% Sertraline Compound*	% HPMC K100LV[1]	% HPMC K4M[2]	% Lactose	% MgSt[3]	Tablet Weight (mg)
4P	30.0	20.0	10.0	38.0	2.0	375
4Q	15.0	24.4	12.2	46.4	2.0	750
4R	30.0	15.0	15.0	38.0	2.0	375
4S	15.0	18.3	18.3	46.4	2.0	750
4T	30.0	33.3	16.7	18.0	2.0	375
4U	15.0	40.6	20.4	22.0	2.0	750
4V	30.0	26.6	13.4	28.0	2.0	375
4W	15.0	32.5	16.3	34.2	2.0	750
4X	15.0	30.5	6.1	46.4	2.0	750

[1] HPMC means hydroxypropyl methylcellulose, Methocel K100LV (Dow Chemical, Midland, MI)

[2] HPMC means hydroxypropyl methylcellulose, Methocel K4M (Dow Chemical, Midland, MI)

[3] MgSt means magnesium stearate

* % sertraline compound reflects quantity of sertraline salt needed to achieve 200 mgA.

Table 4-3

Sustained Release Hydrophilic Matrix Tablet Compositions Manufactured by Direct Compression on the F-Press with Dosage Strength of 50mgA/tablet.

Example	% Sertraline Compound*	% HPMC K100LV[1]	% HPMC K4M[2]	% Lactose	% MgSt[3]	Tablet Weight (mg)
4Y	30.0	20.0	10.0	38.0	2.0	187.5
4Z	15.0	24.4	12.2	46.4	2.0	375
4AA	15.0	18.3	18.3	46.4	2.0	375
4AB	15.0	40.6	20.4	22.0	2.0	375
4AC	15.0	32.5	16.3	34.2	2.0	375
4AD	15.0	30.5	6.1	46.4	2.0	375

[1] HPMC means hydroxypropyl methylcellulose, Methocel K100LV (Dow Chemical, Midland, MI)

[2] HPMC means hydroxypropyl methylcellulose, Methocel K4M (Dow Chemical, Midland, MI)

[3] MgSt means magnesium stearate

* % sertraline compound reflects quantity of sertraline salt needed to achieve 200 mgA.

Example 5

Selected sustained release matrix tablets from Example 4, as shown in Table 5-1, were tested using the in vitro sustained release dissolution test procedure with quantification by reverse-phase high performance liquid chromatography (HPLC) analysis for sertraline to determine sertraline released as a percentage of the total dose, as described below.

Sustained release dosage forms of sertraline were tested in a standard USP rotating paddle apparatus as disclosed in United States Pharmacopeia XXIII (USP) Dissolution Test Chapter 711, Apparatus 2. Paddle rotation was set at 50rpm and the dissolution was conducted in, as the test medium, 900 mL acetate buffer (0.13M acetic acid) with 0.075M sodium chloride using potassium hydroxide to adjust pH to 4.0, at 37°C. The dissolution vessels were covered to prevent evaporation. At indicated times following test initiation (i.e. insertion of the dosage form into the apparatus vessel), filtered aliquots (typically 2 or 10mL) from the test medium were withdrawn and analyzed for sertraline by reverse-phase HPLC as disclosed below.

Sertraline quantification was conducted by reverse-phase high performance liquid chromatography as follows. A fixed volume of 20 µL was injected onto the analytical column (150 mm length x 3.9 mm diameter Nova-Pac C-18 column). The isocratic mobile phase consisted of an aqueous acetate buffer, methanol and acetonitrile in volume percentages of 40/15/45. The aqueous acetate buffer was prepared by the following: (1) 2.86 mL of glacial acetic acid was added to a 1000 mL Erlenmeyer flask with a magnetic stir bar in an ice bath; (2) while stirring, 3.48 mL of triethylamine was added to the flask; and (3) the flask was filled to volume and mixed well. To the aqueous acetate buffer (40 %) was added HPLC-grade methanol (15 % v/v) and HPLC-grade acetonitrile (45 % v/v). After mixing well, the mobile phase was vacuum filtered and degassed using a 0.45µm PTFE filter (Lid-X 305 disposable solid liquid separators). The mobile phase flow rate was 1.8 mL/min with sertraline UV detection at 254nm.

Dissolution results reported as the percent of sertraline dissolved versus time are presented in Table 5-1 (n=3 tablets). Examples 4P, 4Q, 4V, 4X, 4Z, 4AB, 4AC, and 4AD satisfied the dissolution criteria and are sustained release embodiments of

this invention. The other formulations from Tables 4-1, 4-2, and 4-3 were not tested, but are also sustained release embodiments of this invention.

Table 5-1

In Vitro Sertraline Sustained Release from Hydrophilic Matrix Tablet Compositions Designated in Table 4-1, 4-2 and 4-3

Example	Q_1 (%)	Q_4 (%)	Q_8 (%)	Q_{12} (%)	Q_{16} (%)	Q_{24} (%)
4P	13.2	26.6	41.4	56.1	70.0	89.7
4Q	9.6	20.4	32.4	47.8	60.2	75.2
4V	6.3	20.9	40.2	54.0	65.1	82.1
4X	8.9	24.8	44.1	61.3	73.7	92.2
4Z	11.3	25.8	43.0	59.0	73.3	88.4
4AB	5.0	16.4	28.7	40.4	51.9	70.7
4AC	5.7	19.6	37.3	54.9	70.4	92.2
4AD	9.6	28.5	52.0	72.4	86.2	96.8

Q = reported values of % drug released represents the average of 3 tablets

Example 6

This example demonstrates that certain sertraline side effects (e.g. nausea, regurgitation, and diarrhea) are partially or primarily mediated by direct contact of orally dosed sertraline with the upper gastrointestinal tract, rather than mediated by the presence of sertraline in the systemic circulation after absorption. Bypassing the stomach by dosing sertraline orally in a dosage form which exhibits delayed release before sustained release (i.e., a delayed plus sustained release dosage form) can thus further ameliorate the locally mediated side effects of sertraline.

In a subset of a larger double-blind, randomized, placebo-controlled parallel group study, healthy male human subjects were divided into two groups (Study I). Group A received a single 200 mg sertraline dose as two 100 mg sertraline tablets (Zoloft commercial 100 mg tablets) ("bolus dosing" group). The tablets were administered with 50 ml water. Group B received two placebo tablets. All subjects were dosed after an overnight fast.

Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 240 hr post-dosing. Plasma sertraline concentrations were determined using

capillary gas chromatography. Total systemic exposure to sertraline was determined by measuring the area under the plasma sertraline concentration vs. time curve (AUC) for each subject in a given group, and then by calculating a mean AUC for the group. C_{max} is the maximum observed plasma sertraline concentration achieved in a subject. T_{max} is the time at which C_{max} is achieved. After the 200 mg sertraline dose, average C_{max} was 74 ng/ml, average T_{max} was 6 hr, and average AUC was 1646 ng-hr/ml (averaged for 15 subjects).

A similar second study was carried out (Study II). After the 200 mg sertraline dose, average C_{max} was 75 ng/ml, average T_{max} was 5.4 hr, and average AUC was 1744 ng-hr/ml (averaged for 11 subjects). Four subjects in the 200 mg dose group had emesis at 2.6, 2.8, 2.8, and 3.8 hr. The data from these four subjects were not included in the pharmacokinetic averages.

Prior to dosing and each blood sampling time, each subject filled out a questionnaire, which consisted of a series of "Visual Analogue Scales" in which the subject was required to rate, on a scale of 0-10, the severity of certain potential side effects. The subjects were instructed that "0" indicated an absent effect and "10" indicated the worst possible effect. The subjects were instructed to interpolate between 0 and 10 for moderate side effects.

A total of 30 subjects completed Study I: 15 each in Groups A and B. For each side effect evaluated at 30 time points, a total of 900 individual visual-analogue-scale evaluations were obtained. A total of 29 subjects completed Study II: 14 in Group A and 15 in Group B. For each side effect evaluated at 30 time points, a total of 870 individual visual-analogue-scale evaluations were obtained.

Figure 6 presents the relationship between plasma sertraline concentration and average self-reported visual analogue score for nausea in Study I. This plot, known as a pharmacokinetic-pharmacodynamic relationship plot ("PK/PD Plot"), was obtained as follows. For the 15 subjects in Group A, plasma sertraline concentration was averaged at each blood collection timepoint, to give an average sertraline concentration for Group A at each time point. Likewise, for the 15 subjects in Group A, the visual analogue score for nausea was averaged at each time point. The average nausea scores at each time point (y-axis) were plotted vs.sertraline plasma levels at the corresponding time point (x-axis). The arrow on the plot demonstrates the progression of the PK/PD relationship as time progressed. The PK/PD plot of

Figure 6 exhibits "clockwise hysteresis" for the 200 mg bolus dose. Thus as time progressed, the nausea score and the plasma sertraline concentration both increased until the nausea score reached a maximum value, at a plasma sertraline concentration which was below the maximum plasma sertraline concentration C_{max}. As C_{max} was reached (at ~70 ng/ml), the nausea score fell to a lower value. As the subsequent plasma sertraline concentrations fell, the nausea score assumed values which were lower than the scores observed for the same plasma sertraline concentrations at earlier timepoints. This "clockwise hysteresis" (or "proteresis") is consistent with the interpretation that sertraline-induced nausea is significantly mediated by direct contact of sertraline with the GI tract, and is not entirely mediated by the presence of sertraline in the systemic blood, since the average nausea score is not monotonically related to plasma sertraline concentration. At early time points after dosing (0-3 hr), orally dosed sertraline is primarily in contact with the stomach. Since nausea is not directly monotonically related to plasma sertraline concentration, and is apparently primarily mediated locally by contact with the gastrointestinal tract, releasing sertraline lower in the gastrointestinal tract, e.g. the duodenum or jejunum, will result in decreased contact time with the upper gastrointestinal wall, and thus less nausea.

In Study 1, diarrhea was also shown to exhibit clockwise hysteresis in its side effect score vs. plasma sertraline concentration curve. The maximum diarrhea score was reached at 3hr post-dose, long before the observed average plasma T_{max} of 6 hr in these subjects. Thus delaying the release of orally dosed sertraline until the stomach is passed may result in less diarrhea.

As described above, in Study 2, four subjects exhibited regurgitation. Individual PK/PD plots for these subjects, for the side effect regurgitation, exhibited clockwise hysteresis. Thus delaying the release of orally dosed sertraline until the stomach is passed may result in less regurgitation.

Example 7

This example illustrates a process for making sustained release sertraline multiparticulates according to the invention. The process for making sustained release sertraline multiparticulates consisted of preparing uncoated sertraline multiparticulate cores by rotary granulating with microcrystalline cellulose as

spheronizing agent and water as a granulating agent until a mean granule size of >1mm was achieved.

Sertraline multiparticulates were prepared using a fluid bed processor with rotor insert (Glatt GPCG-1 by Glatt Air Techniques, Ramsey, NJ). The rotor bowl was charged with 300 grams of sertraline drug and 300 grams of microcrystalline cellulose as spheronizing agent. Then, water was tangentially sprayed into the rotating bed of drug and microcrystalline cellulose until the agglomeration endpoint (defined by the mean granule size) was reached. After the granulation was completed, the multiparticulates were dried in the rotary fluid bed until their water content was less than 2% (measured by weight loss on drying or LOD). The composition and key process parameters of these multiparticulates are listed in Table 7-1.

Table 7-1

Sustained Release Sertraline Multiparticulate
Composition and Key Manufacturing Parameters
Employed During Rotary Granulation Processing

Example No.	Sertraline* (grams)	Avicel (grams)	Water (grams)	Rotor Speed (rpm)	Spray Rate (g/min)	Endpt LOD (% H2O)	Mean Granule Size (µm)
7A	300	300	1100	640	15-20	49	1200

* sertraline quantities in terms of hydrochloride salt form

Example 8

This example illustrates a process for making sustained release sertraline multiparticulates according to the invention that release at different rates depending on the thickness of the sustained-release coating. The process comprises (1) preparing uncoated sertraline multiparticulate cores by rotary granulating with or without microcrystalline cellulose as a granulating agent and water or a binder solution; and (2) applying a rate-limiting coating over the cores. This example further evaluates the release profile of the sustained release multiparticulates.

Sertraline multiparticulates were prepared using a fluid bed processor with rotor insert (Glatt GPCG-1 by Glatt Air Techniques, Ramsey, NJ). The rotor bowl

was charged with 300-500 grams of sertraline drug and 0-500 grams of microcrystalline cellulose as spheronizing agent. Water, plasticized hydroxypropyl methylcellulose (Opadry™) or polyvinylpyrrolidone (Povidone C15) binder solution (10% solids concentration) was tangentially sprayed into the rotating bed until the agglomeration endpoint (defined by the mean granule size) was reached. The target mean granule size was varied from 100 to 1400µm during the manufacturing of these formulations. After the granulation was completed, the final multiparticulates were dried in the rotary fluid bed until their moisture content was less than 2% (measured by loss on drying, LOD). A summary of the compositions of multiparticulates manufactured using water as the granulating agent are detailed in Table 8-1 for Examples 8A through 8F. A summary of the multiparticulate core compositions, manufacturing parameters and final mean granule size produced during the manufacture of the formulations that utilized a binder solution consisting of either an aqueous Opadry or Povidone solution as granulating agent are shown in Table 8-2 for Examples 8G-8S.

Table 8-1

Sertraline Multiparticulate Core Compositions
and Manufacturing Parameters Employed During
Rotary Granulation Processing Using Water as Granulating Agent

Example No	Sertraline (grams)	Avicel (grams)	Water (grams)	Rotor Speed (rpm)	Spray Rate (g/min)	Endpt LOD[b] (% H2O)	Mean Granule Size (µm)
8A	300	300	1340	640	13	39	320
8B	300	300	1340	640	12	41	470
8C	500	500	2950	640 - 585	13-15	42	465
8D	335	165	630	630	14	36	510
8E	300 [a]	300	700	630	13	37	370
8F	300	300	1060	630	12	45	600

(a) jet milled sertraline hydrochloride <10µm
(b) LOD - Loss on drying

Table 8-2

Sertraline Multiparticulate Core Compositions
and Manufacturing Parameters Employed During
Rotary Granulation Processing Using a Binder Solution as Granulating Agent.

Example No	Sertraline (grams)	Avicel (grams)	Binder (10%)	Rotor Speed (rpm)	Spray Rate (g/min)	Outlet Temp (oC)	Air Velocity (Pa)	Mean Granule Size (µm)
8G	500	0	OC	640	5-15	33	10-14	530
8H	500	0	OC	640	5	34	10	130
8I	500	0	OC	640	5	32	10	205
8J	500	0	OC	640	10	27	12	270
8K	400	100	OC	640	15	30	13	320
8L	375	125	OC	800	26	31	20	680
8M	375	125	OC	810	21	37	10	340
8N	375	125	PVP	800	25	33	8	n.d.
8O	375	125	OC	855	24	36	8	1400
8P	375	125	OC	855	25	37	8	390
8Q	375	125	OC	855	24	36	10	510
8R	375	125	OC	855	24	37	12	360
8S	375	125	OC	855	24	36	11	430

OC means Opadry™ Clear, plasticized hydroxypropyl methylcellulose
PVP means Povidone C15, plasticized polyvinylpyrrolidone

Next, the sertraline multiparticulate core granules (Example 8D) were spray coated with a rate-limiting coating in the rotary fluid bed (Glatt GPCG-1, Glatt Air Techniques, Ramsey, NJ) until the desired end point (coating weight %) was achieved. In this example, the rate-limiting coating was composed of plasticized ethylcellulose (Surelease™) suspension diluted to 25% solids and hydroxpropyl methylcellulose (Opadry™, Colorcon, Inc.) in weight ratios of 85% Surelease™ to 15% Opadry™. This coating was applied to the multiparticulate core granules manufactured according to this Example to coating levels ranging from 5 wt% to 25 wt%.

Example 9

This example illustrates the process for making a sustained release sertraline non-erodible matrix tablet. The processing comprises of (1) blending all components except for magnesium stearate; (2) screening and reblending the same components; (3) adding and blending magnesium stearate; and (4) compressing the final blend

into tablets. This example further evaluates the *in vitro* release profile of sertraline from the matrix tablets using the *in vitro* test described in the specifications.

In a batch size of 100 grams, sertraline was blended in a suitable jar with all other components except magnesium stearate for 10 minutes using a Turbula shaker system (Basel, Switzerland). Next, the blend was passed through a 40 mesh screen and reblended for 5 minutes. Then, magnesium stearate was added to the mixture and blended for 5 minutes. Using the Manesty F-Press (Manesty Machines, Liverpool, England), the final blend was compressed into tablets using conical tablet tooling punches with top-to-base diameter ratio of 1:3 and height-to-base ratio of 2:5. A summary of the composition manufactured by direct compression of the formulation blend at 127mgA sertraline per tablet is shown in Table 9-1.

Table 9-1

Sustained Release Non-erodible Matrix Tablet
Composition Manufactured by Direct Compression
on the F-Press with Dosage Strength of 127mgA/tablet

% Sertraline Compound*	% Ethocel[1]	% Lactose	% MgSt	Tablet Weight (mg)
33.7	40.0	24.3	2.0	420

[1] Ethocel™, Ethylcellulose NF Standard Premium, viscosity 10, Dow Chemical

* sertraline compound quantities in terms of hydrochloride salt form

Finished sustained release non-erodible matrix tablets were tested using the *in vitro* sustained release dosage test procedure described in Example 5. The results are presented in Table 9-2 (n=1 tablet). This non-erodible matrix tablet satisfies the dissolution criteria and is a sustained release embodiment of this invention.

Table 9-2

In Vitro Sertraline Sustained Release from
Non-erodible Matrix Tablet Composition Designated
in Table 9-1 into 900mL 0.13M acetate buffer with
0.075M sodium chloride, pH 4.0 at 37°C in USP Apparatus #2
with Paddle Speed Setting of 50rpm

Q_1 (%)	Q_4 (%)	Q_8 (%)	Q_{12} (%)	Q_{16} (%)	Q_{24} (%)	Release Rate† (mgA/hr)
6.2	13.9	23.1	28.5	33.8	41.2	2.2

Q = reported values of % drug released represents one tablet
† means that sertraline release rate was calculated based on the 24 hr timepoint because 80% release did not occur within the 24 hr testing period.

Example 10

This example illustrates that organic acids have the ability to raise the solubility of the hydrochloride salt of sertraline. The acids were screened by dissolving the candidate acid in water and then stirring excess sertraline hydrochloride in the acid solution for at least 8 hours. The concentration of sertraline in the supernatant was then measured by HPLC analysis. The results of this test are listed in Table 10-1, below. Most of the acids listed in the table successfully raised the solubility of sertraline hydrochloride (normal solubility 2.5 mg/ml).

Table 10-1

Excipient	Approximate Excipient Concentration (mg/ml)	Sertraline Solubility (mg/ml)
D,L-malic acid	900	21
Citric acid	600	20
Erythorbic acid	400	19
Adipic acid	14	12
Maleic acid	700	6.4
L-aspartic acid	10	5.5
Tartaric acid	1400	5.5
L-glutamic acid	12	5.4
Fumaric acid	11	3.1
Tannic acid	2000	2.8
D,L-tyrosine	600	2.2

Preferred acids, based on this screening test, are malic, citric, erythorbic, and adipic acids. Maleic, L-aspartic, tartaric, and L-glutamic acids also significantly improved sertraline hydrochloride solubility. Some controlled-release dosage forms with such acids in the core will perform better than those without such acids. This is particularly true for osmotic-based formulations that deliver a solution of drug.

Example 11

This example illustrates that organic acids have the ability to raise the solubility of the acetate salt of Sertraline by a method similar to that used for the hydrochloride salt described in Example 10. The excipient, excipient concentration, and sertraline solubility are listed in Table 11-1 below. Based on these results, preferred acids to include in a dosage form where increased Sertraline acetate solubility is desired are ascorbic, erythorbic, citric, lactic, aspartic, glutamic, and aconitic acids.

Table 11-1

Excipient	Excipient Concentration (mg/ml)	Sertraline Solubility (mg/ml)
Ascorbic acid	400	>425
Erythorbic acid	400	>330
Citric acid	600	146
Lactic acid	213	>294
Aspartic acid	7	110
Glutamic acid	12	108
Aconitic acid	500	>92
Itaconic acid	150	72
Succinic acid	77	28
None	–	64

Example 12

This example illustrates that organic acids and three calcium salts have the ability to raise the aqueous solubility of the lactate salt of sertraline using a method similar to that used for the hydrochloride salt described in Example 10. The excipient, the excipient concentration in the aqueous test solution, and the Sertraline lactate solubility in the test solution are listed in Table 12-1 below. Solubility of Sertraline lactate in water is approximately 125 mg/ml. The data below show that

eight organic acid solutions had sertraline lactate solubilities of about the same or higher than 125 mg/ml; adipic, erythorbic, itaconic, citric, aspartic, glutamic, histidine, and ascorbic. Also, a solution of a mixture of two of these acids also had high solubility; ascorbic and aspartic. Sertraline lactate solubility was also high in calcium salt solutions, either alone (calcium citrate) or mixed with ascorbic acid.

Table 12-1

Excipient	Excipient Concentration (mg/ml)	Sertraline Lactate Solubility (mg/ml)
Adipic acid	14	360
Erythorbic acid	400	>217
Itaconic acid	150	>202
Citric acid	600	162
Aspartic acid	7	>155
Glutamic acid	12	>125
Histidine	42	>116
Ascorbic/Aspartic	400/7	116
Ascorbic	400	102
Glycine	250	66
Aconitic acid	200	<59
Tartaric acid	1400	12
Fumaric acid	11	<9
Sorbic acid	3	<9
Calcium lactate/ Ascorbic acid	50/400	160
Calcium citrate	10	165
Calcium carbonate/ Ascorbic acid	50/400	176
None	–	125

Example 13

The lower solubility of the sertraline chloride salt and of all sertraline lactate and sertraline acetate salts in the presence of high chloride concentrations suggest that core formulations are preferred for which sertraline stays in solution that is, it does not precipitate or form a gel-like material when chloride is present. Certain organic acids and salts were found to inhibit precipitation or gelation of Sertaline when chloride is present via the following screening test. Sertraline lactate was dissolved in water either alone (as a control) or with a candidate excipient. Sodium chloride was then added (as a concentrated solution) and the result observed. An

excipient was considered beneficial if the solution remained clear and fluid. The more chloride that could be added to an excipient solution with the solution remaining clear, the more beneficial was the excipient. Table 13-1 below shows the results of this screening test, indicating that all the excipients tested increased sertraline concentration in the chloride solutions.

Table 13-1

Excipient	Excipient Concentration (mg/ml)	Concentration NaCl (mM)	Final Sertraline Concentration (mg/ml)	Observation After NaCl Addition
None	--	38	22	gel/precipitate
Ascorbic/ Aspartic acids	400/7	152	162	solution
Aspartic acid	7 7	114 152	162 100	solution gel
Ascorbic acid	400	100	102	precipitate
Ascorbic acid/ calcium lactate	400/50	150	165	solution
Ascorbic acid/ calcium carbonate	400/50	150	170	slightly turbid
Citric acid/ calcium lactate	600/50	150	162	solution
Histidine	42	150	110	slight precipitate

Example 14

Organic compounds (solubilizers) were screened for their ability to enhance the solubility of sertraline lactate in aqueous solutions with or without the presence of chloride. Excess sertraline lactate was added to an aqueous solution of the candidate solubilizer and, in most cases an organic acid. The organic acids were saturated in these solutions and the additional solubizing agents were at the concentration shown in Table 14-1. The equilibrium sertraline solubility was measured. Then, sodium chloride was added to the saturated solution and the final sertraline concentration was measured. The results of these screening tests are summarized in Table 14-1.

Table 14-1

	Solubilizer	Solubilizer Concentration (mg/ml)	Organic Acid	Sertraline Solubility (mg/ml)	NaCl Concentration (mM)	Sertraline Concentration (with NaCl)
1	None (control)	-	none	125	150	5
2	Monocaprylin	10	ascorbic	160	150	160
3	Triacetin	100	ascorbic	170	150	170
4	Monobutyrin	50	none	120	150	120
5	Diacetin	50	ascorbic	120	150	120
6	Imwitor® 312	10	ascorbic	120	150	120
7	Imwitor® 375	10	ascorbic	120	150	120
8	Imwitor® 742	50	none	120	150	120
9	Imwitor® 988	50	none	140	100	140
10	Triethyl citrate	50	ascorbic	160	150	160
11	Pluronic® L31	50	none	120	100	120
12	Cremophore EL	50	ascorbic	120	150	120
13	Sucrose acetate isobutyrate	50	ascorbic	120*	150	120
14	Sodium capryl lactate	50	ascorbic	120	150	120
15	Sucrose monolaurate	50	none	150	150	150
16	Sodium lauryl lactate	50	ascorbic	120	150	120
17	Span® 80	50	ascorbic	120	150	120

Example 15

This example illustrates that solubilizers for sertraline also can increase the rate of dissolution of sertraline. The effect of a candidate excipient on sertraline dissolution rate was determined by adding solid drug, the candidate solubilizing excipient, and, in some cases, other excipients such as an organic acid and an osmagent (such as a sugar) to a 1.8 ml centrifuge tube. The sample tubes were spun at 14K G for 5 minutes in a microcentrifuge to pack the powder. 150 µl gastric buffer was added to the packed powder and the samples were gently agitated, then spun at 14K G in a microcentrifuge for 2 minutes. The samples were then removed from the microcentrifuge and allowed to stand undisturbed until the solution was removed. The solution was removed from the samples after a total of 10 minutes after gastric buffer was added to the powder pack, and analyzed by HPLC to determine the sertraline concentration.

The dissolution rate (mg sertraline/ml-min) was calculated from the measured concentration of dissolved sertraline in the supernatant as a function of time over the first 10 minutes of dissolution. These dissolution rates and the excipient mixtures for which they were measured are summarized in Table 15-1 below. As shown, several excipient mixtures containing solubilizers significantly (about 3X or greater) increased the dissolution rate of sertraline, compared with sertraline alone and compared with sertraline and ascorbic acid.

Table 15-1

Candidate Excipient		Organic Acid	Organic Acid Conc. (wt%)	Osmagent	Osmagent Conc. (wt%)	Other Excipient	Other Excipient Conc. (wt%)	Sertraline Salt Form Conc. (wt%)	Sertraline Dissolution Rate (mg/ml-min)
Name	Concentration (wt%)								
None	--	none	--	none	--	none	--	lactate 100	0.9
None	--	ascorbic	51.0	lactose	20	none	--	lactate 14	3.5
Imwitor® 312	5.0	ascorbic	49.5	lactose	12.5	$CaCO_3$	5	lactate 14	20.9
Lecithin	5.0	ascorbic	51.0	lactose	15	none	--	lactate 14	10
PEG 3550	5.0	ascorbic	51.0	lactose	15	none	--	lactate 14	9.3
Capmul® MCM	5.0	ascorbic	71.0	none	--	none	--	lactate 24	14.5
Capmul® MCM	4.7	none	none	lactose	17	$CaCO_3$ Ca citrate	4.7 47	lactate 13.1	4.3
Imwitor® 191	5.0	ascorbic	49.5	lactose	12.5	$CaCO_3$	1.0	lactate 14	8.0
Myrerol® (18-99)	5.0	ascorbic	49.5	lactose	12.5	none	--	lactate 14	6.4
Span® 60	5.0	ascorbic	51.0	lactose	15	none	--	lactate 14	9.5
Ascorbyl palmitate	6.8	none	none	lactose	74.2	none	--	lactate 19	4.3

Methyl paraben/ propyl paraben/ propyl gallate	0.5/0.5/1.0	ascorbic	50.0	lactose	17.5	none	--	lactate 14	11.5
Imwitor® 312	6.8	aspartic	74.2	none	--	none	--	lactate 19	5.3

Example 16

This examples illustrates a method for making osmotic tablets comprising a tablet core containing sertraline surrounded by a semipermeable asymmetric membrane coating. Sertraline-hydrochloride was triturated by hand for 10 minutes with citric acid and microcrystalline cellulose (Avicel PH 102, FMC) using a 6 1/2 inch diameter mortar and pestle. Magnesium stearate was then blended in as a lubricant by stirring with a spatula for 60 seconds. The weight ratio of Sertraline-hydrochloride to citric acid to microcrystaline cellulose to magnesium stearate was 8.5:63.8:23.7:4; with a total weight of 10 grams. The blended mixture was pressed into 470 mg tablets in a modified hydraulic jack (manufactured by Dayton) fitted with a pressure gauge and 3/8 inch concave punch under 2500 PSI pressure for 2 seconds. The dimensions of the resulting tablets were 3/8 inch in diameter and 1/4 inch thick. A semipermeable membrane coating (as described in US Patent Application No. 397,974, allowed 10/6/96, entitled The Use of Asymmetric Membranes in Delivery Devices) was applied to these tablets using a LDCS-20 pan coater (Vector Corp.) at a spray rate of 20 grams per minute, an inlet temperature of 40C and air flow of 40 cfm. The coating solution contained by weight 10 % Cellulose acetate, (Eastman Chemical, CA398-10), 2.5% polyethylene glycol (BASF, PEG 3350), 15% water and 72.5% acetone. The coated tablets were dried 1 hour at 50C before testing. After drying, the weight of applied coating material was 15.4% of the total weight. These tablets contained a sertraline dose of 50 mgA/tablet.

Example 17

Osmotic delivery tablets were prepared by using essentially the same procedure for making the tablet cores and applying the asymmetric membrane coating to the cores described in Example 16. The composition of the cores and coating solution varied from that used in Example 16 as shown in Table 17-1. Example 16 is listed in Table 17-1 for comparison. Significant core compositional changes shown include: the Sertraline salt form, the type and amount of solubilizer, and the type and amount of osmagent. The amount of binder (Avicel) lubricant (magnesium stearate), and solubilizer were varied as necessary to obtain

good tableting and wetting properties. These tablets contained a sertraline dose of 50 mgA/tablet.

Table 17-1

Example No.	Core Composition												Osmotic Coating Solution				
	Core Weight (mg)	Drug		Acid		Solubilizer		Osmogent		Avicel wt %	Mg St. wt %	Other	Polymer Type	Polymer wt %	PEG wt %	Water wt %	Coating Weight (dry wt %)
		Salt Form	Wt %	Type	Wt %	Type	Wt %	Type	Wt %								
16	470	chloride	12	none		none		lactose	66	20	2	none	CA	10	2.5	15	15.4
17a	470	lactate	14	none		none		lactose	65.4	19.3	1.33	none	EC	6	4	8	1
17b	470	acetate	14	ascorbic	50	none		lactose	20	15	none	Myrj	EC	6	4	10	10.1
17c	470	lactate	14	ascorbic	50	none		lactose	15	21	none	none	EC	6	4	10	10.1
17d	470	lactate	14	citric	50	none		lactose	20	15	none	Tween	EC	6	4	10	9.9
17e	470	lactate	14	aspartic	11	none		fructose	38	29.5	2.5	Ca Acetate	CA	10	2.5	15	11
17f	470	lactate	14	none		Im	5	lactose	66.4	20	2.6	none	EC	6	4	10	10
17g	470	lactate	14	none		Im	5	xylitol	63.5	25	2.5	none	CA	10	2.5	15	15.5
17h	470	lactate	14	ascorbic	50	MC	5	lactose	12.5	12.5	none	Myrj	EC	6	4	10	10.5
17i	470	lactate	14	glutamic	10	MC	5	sucrose	50	15	none	Ca lactate, Myrj	EC	6	4	10	10.5
17j	470	lactate	14	aspartic	11	MC	5	sucrose	53	15		Myrj	EC	6	4	10	10.1
17k	470	lactate	14	ascorbic	32	Im	5	lactose	12	29	3	$CaCO_3$	EC	7	3	6	15.1
17l	470	lactate	14	ascorbic	32	Im	5	lactose	12	29.5	2.6	$CaCO_3$	EC	6	4	10	10.1
17m	470	lactate	14	aspartic	11	Im	5	fructose	36	27	2.5	Ca acetate	CA	10	2.5	15	10.3
17n	470	lactate	14	glycine	25	Im	5	fructose	28.5	25	2.5	none	CA	10	2.5	15	15.9
17o	580	lactate	11.2	ascorbic	36.5	Triacetin	4.2	lactose	16.2	31.1	none	Myrj	EC	6	4	10	10
17p	470.5	lactate	13.9	succinic	37.2	PEG	15.9	lactose	37.9	none	none	Klucel, SLS	EC	6	4	10	10
17q	536	lactate	12.1	ascorbic	44	Capmul	4.4	lactose	12	22.1	1.5	$CaCO_3$	EC	6	4	10	9.9
17r	470	lactate	14	ascorbic	37	Span 60	5	lactose	11.4	25	2.6	$CaCO_3$	EC	6	4	10	9.8
17s	470	lactate	14	ascorbic	37	Lecithin	5	lactose	11.4	25	2.6	$CaCO_3$	EC	6	4	10	9.9
17t	470	lactate	14	ascorbic	32	Im	5	lactose	12	29.5	2.7	$CaCO_3$	EC	7	3	6	17
17u	470	lactate	14	ascorbic	32	Im	5	lactose	12	29.5	2.7	$CaCO_3$	EC	8	4	8	15
17v	470	lactate	14	aspartic	11	Im	5	fructose	36	27	2.5	Ca acetate	CA	10	2.5	15	20
17w	470	lactate	14	aspartic	11	none		fructose	38	29.5	2.5	Ca acetate	CA	10	2.5	15	10

IM = Imwitor 312 Capmul = Capmul MCM Tween = Tween 80 CA = cellulose acetate 398-10

MC = monocaprylin Mg St. = magnesium stearate Klucel = Klucel EF EC = Ethocel S-100

PEG = polyethylene glycol 3350 Myrj = Myrj 52 SLS = sodium lauryl sulfate

Example 18

The rates of release of Sertraline from selected formulations described in Examples 16 and 17 were determined according to the procedures described in Example 5 with the exceptions that 750ml of solution was used in the dissolution apparatus and the stirring speed was 100 rpm. Analysis of Sertraline released was determined by reverse-phase high-performance liquid chromatography (RP HPLC).

The results of release-rate tests performed using these procedures are listed in Table 18-1. The first two formulations listed, 18a and 18b (formulations 16 and 17a), show release rates lower than claimed in this invention and are included as comparison examples. Both of these formulations contain a sertraline salt (hydrochloride or lactate) and only lactose as the osmagent and no solubilizing excipients. Formulations 18c, 18e, and 18h listed in Table 18-1 all contain a solubilizing excipient and all demonstrate sustained release of sertraline and are embodiments of this invention. Formulations 18d, 18f, and 18g are delayed plus sustained release embodiments of this invention. Likewise the remaining formulations in example 17 (17 b-w) are also sertraline formulations that are embodiments of this invention.

Table 18-1

Sertraline Release Test No	Tablets of Example No	Fraction of Drug Released (%) At Specified Time						
		0 Hr	1 Hr	2 Hr	4 Hr	8 Hr	12 Hr	20 Hr
18a	16	0	0	0	0	0	0	0
18b	17a	0	0	1	2	--	10 (17 hr)	12
18c	17e	0	6	15	35	62	76	78
18d	17j	0	0	0	4	19	28	44
18e	17m	0	8	19	37	60	73	83
18f	17n	0	0.7	6	17	37	54	78
18g	17v	0	0.4	4	13	31	41	53
18h	17w	0	8	18	38	56	64	66

Example 19

This example illustrates osmotic-based sertraline tablets that consist of an inner core containing an osmagent and solubilizing excipient surrounded by a sertraline and excipient layer and then surrounded by a semipermeable coating. The tablets of this example varied from the other examples in that an inner core containing acid, binder and solubilizer was made, tableted, and placed inside a larger drug containing tablet. Citric acid and microcrystalline cellulose (Avicel, PH 102, FMC) were triturated by for 5 minutes using a 4 1/2 inch diameter mortar and pestle. Polyoxyethylene 40 monostearate (Myrj 52, BASF) was then added and triturated for 1 minute. The weight ratio of citric acid to microcrystalline cellulose to Myrj was 86.1:9.8:4.1, with a total weight of 4 grams. The blended mixture was pressed into 232 mg tablets as in Example 16 except that the tablet punch was 1/4 inch. The resulting tablet core was 1/4 inch in diameter and 1/4-inch thick. The blend for the outer tablet was prepared like Example 17. It contained sertraline lactate, citric acid, lactose, Avicel, and polyoxyethylene sorbitan (Tween 80, ICI) in a weight ratio of 14:50:20:15:1. The final tablet was made by placing 200 mg of the drug containing blend into the bottom of the standard 3/8-inch die then the 232-mg citric acid tablet was placed on top of this and an additional 270 mg of the drug containing blend poured onto the top. The tablet was then pressed using the same conditions as in Example 16. The dimensions of the resulting tablet were 3/8 inch in diameter by 1/2-inch thick. A semipermeable membrane coating was applied to the tablets using the same method as in Example 16. Results from release rate tests similar to those described in Example 5 indicate that this osmotic formulation of sertraline is an embodiment of this invention.

Example 20

This example illustrates a method for making an osmotic tablet consisting of a bilayer tablet core surrounded by a semipermeable coating. To form the drug containing granulation the following materials are blended and wet granulated in a mixer: 50 to 200 g sertraline and its pharmaceutically acceptable salts; from 250 to 325 g of polyethylene oxide having a molecular weight of about 100,000 and from 0 to 275 g of a polyethylene oxide having a molecular weight of about 200,000; from 10

to 30 g of a hydroxypropylmethylcellulose having an average molecular weight of about 11,300; and from 0 to 10 mg of a magnesium stearate. The second granulation to make the second layer in the tablet core comprises from about 110 to 140 g of a polyethylene oxides having an average molecular weight ranging from about 5,000,000 to 7,500,000; from 5 to 25 g of a hydroxypropylmethylcellulose having an average molecular weight of about 11,300; from 40 to 70 g of sucrose; and, from 0 to 10 g of magnesium stearate. These granulations are used to make a bilayer tablet core with one layer containing sertraline and the second layer mostly swellable hydrophilic materials. These bilayer tablets are then coated with a semipermeable coating comprising 70% to 98% cellulose acetate having an acetyl content of 32% to 39.8%, and from 2 to 30% of polyethylene glycol having an average molecular weight of about 3350. In the coating at least one exit passageway is formed on the sertraline-containing side of the tablet.

Example 21

Osmotic delivery tablets were prepared with a water permeable outer coating through which were drilled delivery ports for the passage of sertraline dissolved in the aqueous solution contained in the tablet core. Tablet cores composed of 14.0 wt% sertraline lactate, 11.0 wt% aspartic acid, 47.4 wt% sucrose, 25.0 wt% Avicel PH 101, and 2.6 wt% magnesium stearate (total core weight was 470 mg) were prepared by essentially the same method given in Example 17. These tablet cores were then coated with a solution composed of 6% ethylcellulose (Ethocel S-100, Dow Chemical), 4 wt% polyethylene glycol (PEG 3350, BASF) and 8 wt% water in acetone using the method described in Example 17 such that the coating weight was 70.4 mg per tablet (total coated tablet weight was 540.4 mg). For some of the tablets, 3 holes, each 340 μm in diameter, were drilled in each face of each tablet (total of 6 holes per tablet). For a second set of tablets, 18 holes, each 340 μm in diameter, were drilled in each face of each tablet (total of 36 holes per tablet).

A tablet of each type was each tested for sertraline release using 0.75 L of acetate/saline buffer as described in Example 5. The percent sertraline released to the receptor solution as a function of time for each type of tablet is shown in Table21-1, below. Both types of tablets showed similar release profiles, indicating that release

of drug is predominately osmotically driven, (if release was predominately diffusional, the tablets with 36 holes should release drug approximately 6 times faster than the tablets with 6 holes).

Table 21-1

Time	Sertraline Released (%)	
(hr)	6-Hole Tablet	36-Hole Tablet
0	0	0
1	3	7
2	12	17
4	26	32
8	44	44
12	47	46

Example 22

This example describes swelling hydrogel controlled release sertraline tablets. Sertraline hydrochloride or acetate or lactate or aspartate (50 mgA sertraline) is blended with 20K molecular weight polyethylene oxide (PEO-20K) (350 mg) with other solubilizers and excipients, and the blend is tabletted on a Manesty Type-F3-press. The tablets are spray-coated with a solution of cellulose acetate in acetone/ethanol, to a final dry weight coating of 14% of the total coated tablet weight. A 2 mm diameter hole is drilled (via mechanical, laser or other means) through the coating on one face of a portion of the tablets. A 2 mm diameter hole is drilled through the entire center of the tablet for another portion of the tablets.

Example 23

This example describes swelling hydrogel controlled release sertraline tablets. Sertraline hydrochloride or acetate or lactate or aspartate (50 mgA sertraline) is blended with 20K molecular weight polyethylene oxide (PEO-20K) (350 mg) with other solubilizers and excipients, and the blend is tabletted on a Manesty Type-F3-press. The tablets are spray-coated with a solution of cellulose acetate/hydroxypropylcellulose (1:1) in a 9:1 acetone/methanol solution, to a final coating weight of 15% of the total coated tablet weight.

Example 24

This example describes swelling hydrogel controlled release sertraline tablets. Sertraline hydrochloride or acetate or lactate or aspartate (50 mgA sertraline) is blended with 100K molecular weight polyethylene oxide (PEO-100K) (350 mg) with other solubilizers and excipients, and the blend is tabletted on a Manesty Type-F3-press. The tablets are spray-coated with a solution of cellulose acetate in acetone/ethanol, to a final dry weight coating of 14% of the total coated tablet weight. A 2 mm diameter hole is drilled (via mechanical, laser or other means) through the coating on one face of a portion of the tablets. A 2 mm diameter hole is drilled through the entire center of the tablet for another portion of the tablets.

Example 25

This example describes swelling hydrogel controlled release sertraline tablets. Sertraline hydrochloride or acetate or lactate or aspartate (50 mgA sertraline) is blended with 20K molecular weight polyethylene oxide (PEO-20K) (350 mg) with other solubilizers and excipients, and the blend is tabletted on a Manesty Type-F3-press. The tablets are spray-coated with a suspension of sucrose (50/60 mesh) in an acetone solution of cellulose acetate (2.5%) and PEG-600 (2.5%). The weight ratio of cellulose acetate to PEG-600 to sucrose in the coating is 1:1:2. The final coating is 15% of the total coated tablet weight.

Example 26

This example describes swelling hydrogel controlled release sertraline tablets. Sertraline hydrochloride or acetate or lactate or aspartate (50 mgA sertraline) is blended with 20K molecular weight polyethylene oxide (PEO-20K) (350 mg) with other solubilizers and excipients, and the blend is tabletted on a Manesty Type-F3-press. The tablets are spray-coated with a 9/1 acetone/methanol solution of cellulose acetate (2.2%) and hydroxypropylcellulose (HPC) (2.2%). The weight ratio of cellulose acetate to HPC in the coating is 1:1, and the final coating is 15% of the total coated tablet weight.

Example 27

This example describes a perforated coated sustained release sertraline tablet formulation which releases sertraline through a central hole. Sertraline hydrochloride or acetate or lactate or aspartate (50 mgA sertraline) is blended with lactose, magnesium stearate, and optionally ethylcellulose and other excipients, and the blend is tabletted on a Manesty Type-F3-press. The tablets are coated with a solution of ethylene vinyl acetate in methanol. After drying, the coating weight is 15% of the total weight of the uncoated tablets. A 2 mm diameter hole is drilled (via mechanical, laser or other means) through the coating on one face of a portion of the tablets. A 2 mm diameter hole is drilled through the entire center of the tablet for another portion of the tablets. The sertraline release rate is varied by varying the ethylcellulose content of the tablet.

Example 28

This example describes preparation of a pH-triggered (enteric-coated) spatially delayed plus sustained release sertraline tablet. Sertraline sustained release matrix or osmotic or coated hydrogel tablets tablets are prepared as in Examples 4, 9, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26 and 27.

A coating formulation is prepared according to the formulation in Table 28-1.

Table 28-1

Coating Formulation

COMPONENT	FUNCTION	6 WT%
Eudragit L30D-55	enteric polymer	16.0
triethyl citrate	plasticizer	1.6
Talc	detackifying agent	4.0
water	solvent	78.4

The coating solution is sprayed onto sertraline sustained release tablets using a Freund HCT-30 Hi-Coater. Coats [Eudragit polymer + triethyl citrate + talc] are applied ranging from 5-25% of the uncoated tablet weight. These coated tablets release little or no sertraline at the pH of the stomach, and release sertraline in a sustained manner (1 mgA/hr to 40 mgA/hr) after moving into the duodenum.

Example 29

This example illustrates a process for making pH-triggered spatially delayed plus sustained release sertraline multiparticulates.

Sustained release sertraline multiparticulates are prepared as described in Examples 7 and 8. A Wurster bottom spray fluid bed processor (Glatt GPCG-1) is used to apply a delayed release coating. Typical delayed release coating levels are ~5% to ~50%. The delayed-release coating is a suspension containing 12.3% methacrylic acid copolymers (Eudragit® L 30 D-55), 6.2% talc, 1.5% triethyl citrate and 80% water.

Because the delayed release coating is soluble in environments where the pH is greater than 5.5, the multiparticulates thus prepared prevent release of sertraline from the coated particle cores in the stomach, where the pH is low, and permit release of sertraline from the coated particle cores in the small intestine and color, where the pH is greater than 5.5.

Example 30

This example illustrates a process for making pH-triggered spatially-delayed plus sustained release sertraline multiparticulates, with a protective layer between the sustained release multiparticulate core and the pH-triggering delayed release membrane. This dosage form design ameliorates any physical or chemical incompatabilities between the sustained release core and the delayed-release membrane. The process comprises (1) preparing sustained release sertraline multiparticulate cores; (2) applying a protective coat over the core particles; and (3) applying a second , pH-sensitive, delayed release coating over the first coat.

Sustained release sertraline multiparticulate cores are prepared as described in Examples 7 and 8. Using a fluid bed processor, onto the sustained release core particles a solution containing 5 % plasticized hydroxypropyl methylcellulose (Opadry®) solution is sprayed until a coating of 10 % is applied.

A delayed release coating (typically 5 % to 50 % of the final weight of the coated multiparticulates) is applied using the same fluid bed processor as above. The delayed-release coating is a suspension containing 12.3 % methacrylic acid

copolymers (Eudragit® L 30 D-55), 6.2 % talc, 1.5 % triethyl citrate and 80 % water.

Example 31

This example illustrates the preparation of a pH-triggered spatially delayed plus sustained release sertraline coated tablet with a Cellulose Acetate Phthalate Coat.

Sertraline sustained release tablets are manufactured as in Examples 4, 9, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26 and 27. The sustained release tablets are then spray-coated with an acetone solution of cellulose acetate phthalate (CAP) in a HCT-60 Hi-Coater® spray-coating apparatus (Freund Ind. Corp., Tokyo). The CAP is plasticized with 25% (by weight) diethylphthalate (DEP). Sufficient CAP is sprayed onto the tablets to result in a final coating polymer weight, after drying, of 5-50 wt%, relative to the weight of the uncoated tablet bed.

Example 32

This example illustrates the preparation of a pH-triggered spatially delayed CAP-coated sustained release sertraline tablet with a barrier coat.

Sustained release sertraline tablets are manufactured as described in Examples 4, 9, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26 and 27. Tablets are spray coated with a solution of hydroxypropylmethylcellulose (HPMC; Colorcon, Inc.) in water, using a HCT-60 Hi-Coater. In this manner, tablets are coated with a 5 wt% barrier coat of HPMC, relative to the initial sustained release tablet weight. Tablets are then further spray-coated with cellulose acetate phthalate (CAP) and DEP plasticizer (as described in Example 31, in the HCT-60 Hi-Coater. Sufficient CAP is sprayed onto the tablets to result in a final coating polymer weight, after drying , of 5-50 wt%, relative to the weight of the uncoated tablet. The HPMC coat serves as a barrier between the sustained release sertraline tablet and the pH-sensitive CAP coat. This barrier coat prevents premature dissolution (or weakening) of the CAP coat, e.g., in the low pH environment of the stomach, potentially caused by a locally higher pH in the tablet interior due to the presence of sertraline.

Example 33

This example illustrates the preparation of a pH-triggered spatially-delayed (acrylic resin-coated) plus sustained release sertraline tablet with a barrier coat.

Sustained release sertraline tablets are manufactured as described in Examples 4, 9, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26 and 27. Sustained release sertraline tablets are spray coated with a solution of hydroxypropylmethylcellulose (HPMC) (Colorcon, Inc.) in water, using a HCT-60 Hi-Coater. In this manner, tablets are coated with a 5 wt% barrier coat of HPMC, relative to the initial tablet weight.

A coating formulation is prepared according to the formulation in Table 28-1.

The coating solution is sprayed onto HPMC-coated sustained release sertraline tablets using a Freund HCT-30 Hi-Coater.

The total acrylic resin polymer weight applied is 5-50% of the weight of the sertraline sustained release tablet bed. The HPMC undercoat serves as a barrier between sertraline and the pH-sensitive acrylic resin coat. This barrier coat prevents premature dissolution (or weakening) of the acrylic resin coat, e.g., in the low pH environment of the stomach, potentially caused by a locally higher pH in the tablet interior due to the presence of sertraline.

Example 34

This example illustrates preparation of a temporally-delayed (water-activated) plus sustained release sertraline tablet dosage form.

Sustained release sertraline tablets are manufactured as described in Examples 4, 9, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26 and 27. These tablets are then coated with a water-soluble and/or water-disintegrable delay layer, in a tablet coating apparatus such as an HCT-30, HCT-60, or HCT-130 Coater (Freund Inc). The tablets are coated with an aqueous solution of HPMC to a final coating weight of 5-50% of the final weight of the coated tablet. Heavier coating weights give longer delays before initiation of sertraline release into the use environment (the gastrointestinal lumen). The delay time may also be increased by incorporating small to moderate quantities of poorly water-soluble polymers (including but not limited to ethylcellulose (EC), cellulose acetate (CA), cellulose acetate butyrate) into the coating formulation. For example, the coating formulation may consist of 95:5 HPMC/EC to 50:50 HPMC/EC, or 95:5 HPMC/CA to 50:50 HPMC/CA. In the case of

such mixed polymer coating systems, it may be necessary to adjust the solvent composition to dissolve the mixture of water-soluble and poorly water-soluble polymers. For example, mixtures of acetone ethanol and water may be used as needed.

In the environment of use, the dosage forms of this example exhibit a delay in sertraline release, during which time the coating polymer dissolves from the sertraline delayed plus sustained release tablet surface. After the delay, the sertraline sustained release tablet releases its incorporated sertraline at a rate between 1 mg/hr and 40 mg/hr.

Example 35

This example illustrates a method for making osmotic tablets comprising a tablet core containing sertraline-lactate surrounded by a semipermeable asymmetric membrane coating. Tablet cores were made using equipment standard in the pharmaceutical industry. Tablet core components comprising 13.8 wt% sertraline-lactate, 11 wt% L-aspartic acid, 5 wt% calcium acetate, 29.5 wt% microcrystalline cellulose, and 38.2 wt% fructose were blended, then run through a roller compactor and milled. This milled material was then blended with 2.5 wt% magnesium stearate to form the final blended material that was used to make tablets having a total weight of 470 mg on a conventional tablet press (Kilian T-100). Semipermeable asymmetric membrane coatings (as described in U.S. patent 5,612,059) were applied to the tablets using a side-vented pan coater (LDCS-20, Vector Corp.). The coating solution, comprising 10 wt% cellulose acetate 398-10, 2.5 wt% polyethylene glycol 3350, 15 wt% water, and 72.5 wt% acetone, was spray-coated onto the tablets at a rate of 20 g/min until a 10 wt% coating level on the tablets had been achieved.

Example 36

This example illustrates a method for making osmotic tablets comprising a tablet core containing sertraline-lactate surrounded by a semipermeable asymmetric membrane coating. Tablet cores were made using equipment standard in the pharmaceutical industry. Tablet core components comprising 13.8 wt% sertraline-lactate, 5 wt% glyceryl monolaurate, 11 wt% L-aspartic acid, 5 wt% calcium acetate, 27 wt% microcrystalline cellulose, and 35.7 wt% fructose were used to make the

tablet cores. Initially the glycerol monolaurate was wet granulated with 14 wt% microcrystalline cellulose using ethanol (95%) as the wet granulation solvent. After drying and milling, the wet granulate was blended with the components listed above (including the balance of microcrystalline cellulose), then run through a roller compactor and milled. This milled material was then blended with 2.5 wt% magnesium stearate to form the final blended material that was used to make tablets having a total weight of 470 mg on a conventional tablet press (Kilian T-100). Semipermeable asymmetric membrane coatings (as described in U.S. patent 5,612,059) were applied to the tablets using a side-vented pan coater (LDCS-20, Vector Corp.). The coating solution, comprising 10 wt% cellulose acetate 398-10, 2.5 wt% polyethylene glycol 3350, 15 wt% water, and 72.5 wt% acetone, was spray-coated onto the tablets at a rate of 20 g/min. One batch of tablets was made with a 10 wt% coating and a second batch of tablets was made having a 20 wt% coating.

Example 37

Sertraline acetate. Sertraline base (the compound of Preparation AA, 200.2 mg) was dissolved in ethyl acetate (200 µL) in a 5 mL reaction vial. Glacial acetic acid (41.2 µL) was added to the sertraline base solution with constant stirring. An additional 500 µL of ethyl acetate was added to facilitate stirring. The reaction mixture was allowed to granulate at room temperature for five hours. The solids were filtered, washed with 10 mL of ethyl acetate and then dried in a vacuum oven at 40°C for 20 hours. The yield was determined to be 16%. mp 126°C.

Example 38

Sertraline acetate. Sertraline base (the compound of Preparation AA, 200 mg) was dissolved in hexane (1.5 mL) in a 10 mL reaction vial. The solution was heated to 40°C. Glacial acetic acid (41.2 µL) was added to the sertraline base solution. The reaction mixture was allowed to cool to room temperature and then granulate for one hour. The solids were filtered and dried in a vacuum oven at 40°C for 72 hours. The yield was determined to be 90%. mp 126°C.

Example 39

Sertraline acetate. Sertraline hydrochloride (125 g) was slurried in a mixture of water (1 L) and hexane (2.5 L). NaOH (25% aqueous, 35 mL) was added. Sertraline base partitioned into the hexane phase. The hexane layer was separated. The aqueous layer was extracted a second time with hexane (500 mL). The hexane layers were combined. The solution of sertraline base in hexane was heated to 50°C. Glacial acetic acid (23 mL) was added to the solution of sertraline base. The reaction mixture was stirred at 50°C for 30 minutes. The reaction mixture was allowed to cool to room temperature and stirred at room temperature overnight. The crystals were filtered and washed five times with a total of 250 mL of hexane. The solids were dried at 40°C in a vacuum oven for 48 hours. The yield was 89%.
mp 126°C.

Example 40

Single Crystal X-ray Analysis. A representative crystal was surveyed and a 1 Å data set (maximum sin θ/λ= 0.5) was collected on a Siemens R3RA/v diffractometer, Siemens Analytical X-ray Systems, Inc., 6300 Enterprise Lane, Madison, WI 53719-1173. Atomic scattering factors were taken from the International Tables for X-ray Crystallography. International Tables for X-ray Crystallography, Vol. IV, pp. 55, 99, 149 Birmingham: Kynoch Press, 1974. All crystallographic calculations were facilitated by the SHELXTL system. G. M. Sheldrick, SHELXTL User Manual, Nicolet Instrument Corp., 5225 Verona Rd, Madison, WI 53711, 1981). All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table 40-1 below.

A trial structure was obtained by direct methods. This trial structure refined routinely. A difference map revealed a small amount of water located on a two-fold axis. Refinement indicated that the population of this water was 0.25. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogens on nitrogen were located by difference Fourier techniques. The hydrogens on the water were not located. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding

standard deviations. The final R-index was 8.97%. A final difference Fourier revealed no missing or misplaced electron density.

The refined structure, shown in Figure 1, was plotted using the SHELXTL plotting package described in said SHELXTL User Manual. The absolute configuration was not established.

TABLE 40-1

Crystal Parameters of Sertraline-Acetate	
Formula	$C_{17}H_{18}NCl_2^+C_2H_3O_2^-0.25\ H_2O$ (371.3)
Crystallization Medium	water
Crystal size (mm)	0.10 x 0.16 x 0.22
Cell dimensions	a = 15.629(8) Å
	b = 8.695(3) Å
	c = 15.048(3) Å
	α = 90.0°
	β = 110.45(3)°
	γ = 90.0°
	V = 1916(1)Å
Space Group	C2
Molecules/unit cell	4
Density, calculated, g/cm^3	1.287
Linear Absorption Factor, mm^{-1}	3.144

TABLE 40-2. Atomic Coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U (eq)*
C(1)	8321(14)	10711 (22)	-3626 (12)	79 (2)
C(2)	7559(13)	10583 (20)	-3227 (12)	66 (2)
C(3)	7581 (14)	8997	-2770 (12)	83 (2)
C(4)	8453 (11)	8847 (21)	-1902 (11)	67 (2)
C(5)	9260 (11)	9344 (22)	-2182 (12)	66 (2)
C(6)	9268 (14)	10390 (22)	-2917 (12)	87 (2)
C(7)	10033 (16)	10928 (24)	-3028 (14)	103 (2)
C(8)	10898 (14)	10516 (24)	-2347 (14)	91 (2)
C(9)	10883 (16)	9557 (24)	-1637 (14)	97 (2)
C(10)	10115 (12)	9074 (21)	-1513 (12)	67 (2)
C(11)	8555 (14)	7256 (22)	-1473 (14)	79 (2)
C(12)	8418 (12)	6975 (22)	-625 (12)	66 (2)
C(13)	8514 (14)	5542 (25)	-215 (12)	89 (2)
C(14)	8760 (12)	4314 (21)	-708 (18)	90 (2)
C(15)	8861 (18)	4526 (27)	-1587 (15)	132 (2)
C(16)	8763 (14)	6002 (22)	-1905 (13)	88 (2)
N(17)	8112 (9)	9728 (19)	-4522 (10)	65 (2)
C(18)	8616 (14)	10130 (25)	-5161 (13)	98 (2)
C1(19)	8377 (5)	5313 (12)	862 (4)	127 (2)
C1(20)	8816 (6)	2473 (13)	-178 (6)	144 (2)
C(1A)	9993 (16)	5929 (28)	-3685 (16)	157 (3)
C(2A)	9026 (12)	5594 (27)	-4223 (12)	83 (2)
O(3A)	8771 (11)	4331 (19)	-4476 (12)	119 (2)
O(4A)	8464 (12)	6651 (19)	-4306 (11)	116 (2)
O(1W)	10000 (37)	2700 (33)	-5000 (37)	132 (4)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Example 41

Osmotic Tablets of Sertraline Acetate. This example illustrates a method for making osmotic tablets comprising a tablet core containing sertraline acetate surrounded by a semipermeable asymmetric membrane coating. Tablet cores were made using equipment standard in the pharmaceutical industry. Tablet core components comprising sertraline acetate (14 wt%), ascorbic acid (50 wt %), lactose (20 wt%), microcrystalline cellulose (15 wt%) and polyethylene glycol stearyl ether (1 wt%, Myrj 52, Sigma Chemical, St. Louis, MO) were blended by hand using a mortar and pestle. The blended material was used to make tablets having a total weight of 470 mg on a single-station tablet press (F-press). Semipermeable asymmetric membrane coatings (as described in U.S. Patent No. 5,612,059, the teachings of which are incorporated herein by reference) were applied to the tablets using a side-vented pan coater (LDCS-20, Vector Corp., 675 44th St., Marion, IA 52302). The coating solution, comprising ethyl cellulose S-100 (6 wt%), polyethylene glycol 3350 (4 wt%), water (10 wt%), and acetone (80 wt %), was spray-coated onto the tablets at a rate of 20 g/minute until a 10 wt% coating level on the tablets had been achieved.

Example 42

This example illustrates a process for making multiparticulates for use in making delayed-release dosage forms designed to release sertraline predominantly below the stomach. The process comprises (1) preparing uncoated sertraline acetate multiparticulate cores; (2) applying a protective coat over the core particles; and (3) applying a second, pH-sensitive, delayed release coating over the first coat.

Multiparticulate cores containing drug are prepared using a fluid bed processor with rotor insert (Model GPCG-1, Glatt Air Techniques, Ramsey, NJ 07446). The rotor bowl is initially charged with 400 gA of sertraline drug (as sertraline acetate, sertraline lactate or sertraline aspartate) and a binder solution containing 5% poly(ethyl acrylate, methyl acrylate)(Eudragit® NE-30-D), 5% plasticized hydroxypropyl methylcellulose (Opadry®, Colorcon, West Point, PA 19486) and 90% water is sprayed into the rotating bed until an average core granule size of about 250 µm is achieved.

Onto the uncoated core particles in the same fluid bed processor with rotor insert, a binder solution containing 5% plasticized hydroxypropyl methylcellulose (Opadry®) solution is sprayed until a coating of 10% is applied. This intermediate coating enhances the adhesion to the core particles of the final delayed release coating.

A delayed release coating (typically 5% to 50% is required to meet the delayed release criterion) is applied using the same fluid bed processor as above. The delayed-release coating is a suspension containing 12.3% methacrylic acid copolymers (Eudragit® L 30 D-55, Rohm GMBH, Darmstadt, Germany; U.S. Office: Somerset, NJ) 6.2% talc, 1.5% triethyl citrate and 80% water. The final product is a delayed-release multiparticulate with particles having an average size of about 300 µm.

Example 43

Sertraline L-lactate. Sertraline base (the compound of Preparation AA, 200 mg) was dissolved in ethyl acetate (200 µL) in a 10 mL conical reaction vial. L-Lactic acid (solid, 68.5 mg) was separately dissolved in ethyl acetate(100 µL). The L-lactic acid solution was added to the sertraline base solution under constant stirring with a magnetic stirrer. A precipitate was observed within about 2 minutes after complete addition of the L-lactic acid solution to the sertraline base solution. The reaction mixture was allowed to granulate overnight (18 hours) at room temperature. The precipitate was filtered and the solid was rinsed with 1 mL of ethyl acetate. The solid was dried in a vacuum oven at 40°C for 20 hours. The dried solid was characterized and identified as the L-lactate salt of sertraline. The yield was determined to be 72%. mp 153°C.

Example 44

Sertraline L-lactate. Sertraline base (the compound of Preparation AA, 1.0 g) was dissolved in ethyl acetate (20 mL) in a 50 mL round bottom flask and the solution was heated to 40°C. L-Lactic acid (342.5 mg) was separately dissolved in ethyl acetate (5 mL). The L-lactic acid solution was added in small portions to the solution in the round bottom flask which was constantly stirred with a magnetic stirrer. The reaction

mixture was stirred at 40°C for 2 hours after the addition of the L-lactic acid solution was complete. The reaction mixture was then allowed to cool to room temperature and the solids were filtered. The solids were washed with 5 mL of ethyl acetate and then dried under vacuum at 40°C for 24 hours. The dried solid was identified as the L-lactate salt of sertraline. The yield was calculated to be 86%. mp 153°C.

Example 45

Sertraline L-lactate. Sertraline base (10 g) was dissolved in isopropanol (150 mL) in a 500 mL round bottom flask and the solution was heated to 40°C. L-Lactic acid (3.4 g) was separately dissolved in ethyl acetate (25 mL). The L-lactic acid solution was added in small portions to the solution in the round bottom flask which was constantly stirred with a magnetic stirrer. The reaction mixture was stirred at 40°C for 4 hours after the addition of the L-lactic acid solution was complete. The reaction mixture was then allowed to cool to room temperature and the solids were filtered. The solids were washed with 50 mL of hexane and then dried under vacuum at 40°C for 48 hours. The dried solid was identified as the L-lactate salt of sertraline. The yield was calculated to be 94%. mp 153°C.

Example 46

Sertraline L-lactate. Sertraline mandelate (750 grams) was slurried in a mixture of water (3.9 L) and ethyl acetate (3.9 L). The slurry was cooled to 15°C. NaOH (25% aqueous, 250 mL) was added, resulting in a solution with pH 9.6. The free base of sertraline was partitioned into the ethyl acetate layer which was separated. The aqueous layer was extracted with an additional 3.4 liters of ethyl acetate. The combined ethyl acetate layers were washed with 3.9 liters of water. The ethyl acetate layer containing sertraline base was concentrated under vacuum and filtered to clarify the solution. To this solution was added L-lactic acid (155 g). The reaction mixture was granulated for 20 hours at room temperature. The solids were filtered, washed 4 times with ethyl acetate(400 mL each time). The crystals were dried overnight under vacuum at 40°C. The yield was calculated to be 84%. mp 153°C.

Example 47

Sertraline L-lactate. Sertraline hydrochloride (300 g) was slurried in a 3:1 mixture of water (3 liters) and ethyl acetate (1 liter). The pH of the slurry was adjusted to 8.0 by the addition of approximately 1 liter of 1N sodium hydroxide solution. The free base of sertraline partitioned into the ethyl acetate phase. The two phases were allowed to separate completely by allowing the biphasic solution to stand overnight without agitation. The ethyl acetate layer was then separated and washed twice with 3 liters of deionized water to remove chloride ions. The final ethyl acetate layer containing sertraline base was concentrated to 300 mL under vacuum to remove residual water. The ethyl acetate solution containing sertraline base was heated to 40°C. L-Lactic acid was dissolved in ethyl acetate to form a 7.5 M solution. The lactic acid solution was added to the sertraline base solution in small portions with constant agitation. The mixture was allowed to stir and granulate overnight (16-20 hours). The crystals were filtered and washed 4 times with an equal volume (200 mL each) of ethyl acetate. The crystals were dried overnight in a vacuum oven at 40°C. The yield was 97%. mp 153°C.

Example 48

Single Crystal X-Ray Analysis. A representative crystal was surveyed and a 1 Å data set (maximum $\sin\theta/\lambda = 0.5$) was collected on a Siemens R3RA/v diffractometer. Atomic scattering factors were taken from the International Tables for X-ray Crystallography, Vol. IV, Kynoch Press, Birmingham, 1974, pp. 55, 99 and 149. All crystallographic calculations were facilitated by the SHELTXL (see G.M. Sheldrick, SHELTXL. User Manual, Nicolet Instrument Corp., 5225 Verona Rd, Madison, WI 53711, 1981) system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table 48-1.

TABLE 48-1

Crystal Parameters of Sertraline L-lactate	
Formula	$C_{17}H_{18}NCl_2^+C_3H_5O_3^-$ (396.3)
Crystallization Medium	ethyl acetate
Crystal size (mm)	0.07 x 0.07 x 0.11
Cell dimensions	a = 8.660(5) Å
	b = 24.43(1) Å
	c = 9.382(3) Å
	α = 90.0°
	β = 91.94(3)°
	γ = 90.0°
	V = 1984(2)Å^3
Space Group	$P2_1$
Molecules/unit cell	4
Density, calculated, g/cm^3	1.327
Linear Absorption Factor, mm^{-1}	3.101

A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogens on nitrogen and oxygen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 5.49%. A final difference Fourier revealed no missing or misplaced electron density.

The refined structure, shown as Figure 3, was plotted using the SHELTXL plotting package. The absolute configuration was determined by the method of Ibers and Hamilton (Hamilton, Acta Cryst., 1965, 18, 502-510 and Ibers et al., Acta Cryst., 1964, 17, 781-782). The X-Ray absolute configuration was in agreement with the L-lactate configuration. The atomic coordinates are set forth in Table 48-2.

TABLE 48-2. Atomic Coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2x10^3$)

	x	y	z	U (eq)*
C(1)	-4173(13)	4373(5)	7866(10)	44(2)
N(1A)	-4127(10)	3773(4)	7483(9)	47(2)
C(1B)	-5542(14)	3455(6)	7614(12)	69(2)
C(2)	-2556(12)	4576(6)	8220(10)	54(2)
C(3)	-1658(12)	4605(5)	6877(11)	55(2)
C(4)	-2328(12)	5027(5)	5834(10)	44(2)
C(4A)	-4064(12)	4979(5)	5658(10)	45(2)
C(5)	-4860(13)	5273(5)	4565(11)	49(2)
C(6)	-6411(15)	5250(6)	4430(12)	68(2)
C(7)	-7291(13)	4981(6)	5430(13)	68(2)
C(8)	-6563(13)	4705(5)	6491(12)	56(2)
C(8A)	-4955(12)	4700(5)	6662(10)	39(2)
C(1')	-1539(12)	5015(5)	4411(10)	46(2)
C(2')	-1022(12)	5517(5)	3816(12)	52(2)
C(3')	-308(13)	5493(5)	2508(11)	52(2)
C1(1)	243(5)	6117(2)	1757(4)	91(1)
C(4')	-9(13)	5024(6)	1820(11)	54(2)
C1(2)	972(4)	4996	258(3)	81(1)
C(5')	-486(14)	4545(5)	2414(11)	56(2)
C(6')	-1219(14)	4538(5)	3694(11)	52(2)
C(1X)	495(13)	7219(5)	-5303(11)	47(2)
N(1XA)	648(11)	7826(4)	-4926(9)	50(2)
C(1XB)	-814(13)	8109(5)	-4598(12)	58(2)
C(2X)	2126(14)	7016(5)	-5601(12)	67(2)
C(3X)	3130(13)	6938(6)	-4263(11)	64(2)
C(4X)	2437(13)	6525(5)	-3240(10)	53(2)
C(4XA)	702(12)	6586(5)	-3183(11)	46(2)

C(5X)	-45(14)	6304(5)	-2112(12)	55(2)
C(6X)	-1610(15)	6299(5)	-1995(13)	65(2)
C(7X)	-2501(16)	6604(6)	-2945(14)	80(2)
C(8X)	-1807(13)	6890(5)	-4024(12)	56(2)
C(8XA)	-206(12)	6900(5)	-4117(10)	39(2)
C(1X')	3233(13)	6545(5)	-1796(10)	49(2)
C(2X')	3944(14)	6083(5)	-1250(11)	58(2)
C(3X')	4642(13)	6084(5)	101(11)	52(2)
C1(3)	5554(5)	5501(2)	743(3)	85(1)
C(4X')	4732(14)	6569(6)	875(11)	62(2)
C1(4)	5695(4)	6600(2)	2528(3)	78(1)
C(5X')	3978(14)	7023(5)	350(11)	62(2)
C(6X')	3293(15)	7006(5)	-982(11)	63(2)
C(1Y)	1318(16)	2575(6)	9581(14)	106(2)
C(2Y)	540(13)	3113(5)	9839(11)	57(2)
O(3Y)	103(10)	3150(5)	11268(8)	87(2)
C(4Y)	-786(14)	3217(5)	8778(12)	49(2)
O(5Y)	-479(11)	3255(4)	7509(8)	86(2)
O(6Y)	-2081(10)	3239(4)	9294(8)	65(2)
C(1Z)	6352(15)	8746(8)	-2633(15)	110(2)
C(2Z)	4677(13)	8843(6)	-2407(12)	66(2)
O(3Z)	4349(11)	8757(5)	-1000(8)	101(2)
C(4Z)	3602(14)	8483(5)	-3343(11)	50(2)
O(5Z)	3800(10)	8497(4)	-4676(7)	66(2)
O(6Z)	2594(10)	8209(4)	-2782(7)	60(2)

*Equivalent isotropic U is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Example 49

Osmotic Tablets of Sertraline L-Lactate. This example illustrates a method for making osmotic tablets comprising a tablet core containing sertraline L-lactate

surrounded by a semipermeable asymmetric membrane coating. Tablet cores were made using equipment standard in the pharmaceutical industry. Tablet core components comprising sertraline L-lactate (13.8 wt%), L-aspartic acid (11 wt%), calcium acetate (5 wt%), microcrystalline cellulose (29.5 wt%), and fructose (38.2 wt%) were blended, then run through a roller compactor and milled. This milled material was then blended with 2.5 wt% magnesium stearate to form the final blended material that was used to make tablets having a total weight of 470 mg on a conventional tablet press (Killian T-100). Semipermeable asymmetric membrane coatings (as described in U.S. Patent No. 5,612,059, the teachings of which are incorporated herein by reference) were applied to the tablets using a side-vented pan coater (LDCS-20, Vector Corp., 675 44th St., Marion, IA 52302). The coating solution, comprising 10 wt% cellulose acetate 398-10, 2.5 wt% polyethylene glycol 3350, 15 wt% water, and 72.5 wt% acetone, was spray-coated onto the tablets at a rate of 20 g/minute until a 10 wt% coating level on the tablets had been achieved.

Example 50

Osmotic Tablets of Sertraline L-Lactate. This example illustrates a method for making osmotic tablets comprising a tablet core containing sertraline L-lactate surrounded by a semipermeable asymmetric membrane coating. Tablet cores were made using equipment standard in the pharmaceutical industry. The tablet cores were prepared as follows: Glycerol monolaurate (5 wt%) was wet granulated with microcrystalline cellulose (14 wt%) using ethanol (95%) as the wet granulation solvent. After drying and milling, the wet granulate was blended with sertraline L-lactate (13.8 wt%), L-aspartic acid (11 wt%), calcium acetate (5 wt%), microcrystalline cellulose (an additional 13 wt%), and fructose (35.7 wt%). After all of the components were added, the granulate was run through a roller compactor and milled. The milled material was blended with magnesium stearate (2.5 wt%) to form the final blended material that was used to make tablets having a total weight of 470 mg on a conventional tablet press (Kilian T-100, Kilian & Co., 415 Sargon Way Unit 1, Horsham, PA 19044). Semipermeable asymmetric membrane coatings (as described in U.S. Patent No. 5,612,059) were applied to the tablets using a side-vented pan coater (LDCS-20, Vector Corp.). The coating solution, comprising 10 wt% cellulose acetate 398-10, 2.5 wt% polyethylene glycol 3350, 15 wt% water, and 72.5 wt% acetone, was spray-

coated onto the tablets at a rate of 20 g/minute. One batch of tablets was made with a 10 wt% coating and a second batch of tablets was made having a 20 wt% coating.

Example 51

Encapsulated Solution Dosage Form of Sertraline L-Lactate. Solutions of sertraline L-lactate are prepared in Capmul MCM™ (mono- and di-glycerides of caprylic and capric acids, Abitec Corporation, Columbus, Ohio 43219) at a concentration of 75 mgA/mL. The solutions are encapsulated in soft gelatin at a fill volume of 0.67 mL, yielding a unit dose of 50 mgA.

Example 52

Sertraline L-aspartate. Sertraline free base (the compound of Preparation AA, 200.3 mg) was dissolved in ethyl acetate (800µL, which had previously been saturated with water). L-aspartic acid (95.53 mg) was suspended in ethyl acetate (3 mL, which had previously been saturated with water). The aspartic acid suspension was added to the sertraline free base solution. The reaction mixture was stirred for 24 hours. The solids were filtered, washed with ethyl acetate saturated with water and then dried at 40°C in a vacuum oven for 48 hours. The yield of sertraline L-aspartate was 96.4%. mp 247°C.

Preparation AA

Sertraline free base. Sertraline hydrochloride (2.5 grams) was dissolved in water (one liter). To this solution the required amount of 1N NaOH was added until the pH of the solution was adjusted to 8.0. The resulting solids were filtered and washed with deionized water (50 mL per gram of solid). The solids were dried at 40°C in a vacuum oven for 48 hours. The yield was 98%. mp 67°C.

Preparation BB

Sertraline free base. Sertraline hydrochloride (300 g) was slurried in a 3:1 mixture of water (3 liters) and ethyl acetate (1 liter). The pH of the slurry was adjusted to 8.0 by the addition of approximately 1 liter of 1N sodium hydroxide solution. The free base of sertraline partitioned into the ethyl acetate phase. The two phases were allowed to separate completely by allowing the biphasic solution to stand overnight without

agitation. The ethyl acetate layer was then separated and washed twice with 3 liters of deionized water to remove chloride ions. The final ethyl acetate layer containing sertraline base was concentrated to 300 mL under vacuum to remove residual water.

CLAIMS

1. A sustained-release dosage form suitable for oral administration to a mammal, comprising sertraline, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier,

which dosage form releases sertraline into a use environment at a rate not exceeding 0.8 mgA/hr/kg,

provided said dosage form (1) releases not more than 70% of the sertraline contained therein within the first hour following entry into said use environment and (2) releases sertraline at a rate of at least 0.02 mgA/hr/kg.

2. A dosage form as defined in claim 1, wherein said sertraline is present as sertraline free base, sertraline hydrochloride, sertraline aspartate, sertraline acetate or sertraline lactate.

3. A dosage form as defined in claim 1, wherein said mammal is a human.

4. A dosage form as defined in claim 1, in the form of a matrix tablet which remains substantially intact during the period of sustained release.

5. A dosage form as defined in claim 1, in the form of a disintegrating matrix tablet.

6. A dosage form as defined in claim 1, in the form of a matrix tablet partially coated with a polymer which impedes the release of sertraline.

7. A dosage form as defined in claim 1, in the form of an osmotic tablet.

8. A dosage form as defined in claim 1, in the form of a membrane-coated hydrogel tablet.

9. A dosage form as defined in claim 1, which is multiparticulate.

10. A dosage form as defined in claim 1, in the form of a membrane-coated diffusion-based, capsule, tablet or multiparticulate.

11. A sustained-release dosage form suitable for administration to a mammal, comprising sertraline, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier,

which dosage form releases sertraline into a use environment at a rate not exceeding 40 mgA/hr,

provided said dosage form (1) releases not more than 70% of the sertraline contained therein within the first hour following entry into said use environment and (2) releases sertraline at a rate of at least 1 mgA/hr.

12. A dosage form as defined in claim 11 wherein said sertraline is present as sertraline free base, sertraline hydrochloride, sertraline aspartate, sertraline acetate or sertraline lactate.

13. A dosage form as defined in claim 11, wherein said mammal is a human.

14. A dosage form as defined in claim 11, in the form of a matrix tablet which remains substantially intact during the period of sustained release.

15. A dosage form as defined in claim 11, in the form of a disintegrating matrix tablet.

16. A dosage form as defined in claim 11, in the form of a matrix tablet partially coated with a polymer which impedes the release of sertraline.

17. A dosage form as defined in claim 11, in the form of an osmotic tablet.

18. A dosage form as defined in claim 11, in the form of a membrane-coated hydrogel tablet.

19. A dosage form as defined in claim 11, which is multiparticulate.

20. A dosage form as defined in claim 11, in the form of a membrane-coated diffusion-based tablet or multiparticulate.

21. A sustained release dosage form suitable for oral administration to a mammal, comprising sertraline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, which dosage form releases sertraline at a rate less than 40 mgA/hr in vitro when dissolution tested in a USP-2 apparatus containing 900 ml of acetate buffer, pH 4.0, which is 0.075 M in NaCl, as follows:

(1) if said dosage form is a sustained release tablet or a non-disintegrating sustained release capsule, said USP-2 apparatus is equipped with a paddle stirring at 50 rpm;

(2) if said dosage form is a multiparticulate, said USP-2 apparatus is equipped with a paddle stirring at 100 rpm;

provided said dosage form (a) releases not more than 70% of the sertraline contained therein within the first hour following initiation of testing and (b) releases sertraline at a rate of at least 1 mgA/hr.

22. A dosage form as defined in claim 21, wherein said sertraline is present as sertraline free base, sertraline hydrochloride, sertraline aspartate, sertraline acetate or sertraline lactate.

23. A dosage form as defined in claim 21, wherein said mammal is a human.

24. A dosage form as defined in claim 21, in the form of a matrix tablet which remains substantially intact during the period of sustained release.

25. A dosage form as defined in claim 21, in the form of a disintegrating matrix tablet.

26. A dosage form as defined in claim 21, in the form of a matrix tablet partially coated with a polymer which impedes the release of sertraline.

27. A dosage form as defined in claim 21, in the form of an osmotic tablet.

28. A dosage form as defined in claim 21, in the form of a membrane-coated hydrogel tablet.

29. A dosage form as defined in claim 21, which is multiparticulate.

30. A dosage form as defined in claim 21, in the form of a membrane-coated diffusion-based tablet or multiparticulate.

31. A temporally delayed plus sustained release dosage form suitable for oral administration to a mammal, comprising sertraline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier,

which dosage form, following ingestion by said mammal, releases sertraline into said mammal's GI tract at a rate less than 1 mgA/hr for an initial delay period of up to 3 hours,

and which thereafter releases sertraline at a rate of from 1 mgA/hr to 40 mgA/hr, provided said dosage form releases not more than 70 % of the sertraline contained therein within the first hour after said delay period.

32. A dosage form as defined in claim 31, wherein said delay period is up to two hours.

33. A dosage form as defined in claim 31, wherein the rate of release following said delay period is from 1 mgA/hr to 30 mgA/hr.

34. A dosage form as defined in claim 31, wherein said sertraline is present as sertraline free base, sertraline hydrochloride, sertraline aspartate, sertraline acetate or sertraline lactate.

35. A dosage form as defined in claim 31, wherein said mammal is a human.

36. A temporally delayed plus sustained release dosage form suitable for administration to a mammal, said dosage form having an initial temporal delay period of up to 3 hours, comprising sertraline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, which dosage form, when dissolution tested in vitro in a USP-2 apparatus containing 900 ml of acetate buffer, pH 4.0, which is 0.075 M in NaCl,

releases sertraline at a rate less than 1 mgA/hr for a period corresponding to said delay period and, thereafter,

releases sertraline at a rate of from 1 mgA/hr to 40 mgA/hr, provided the dosage form releases not more than 70 % of the remaining sertraline contained therein within the first hour following said delay.

37. A dosage form as defined in claim 36, wherein said delay period is up to two hours.

38. A dosage form as defined in claim 36, wherein the rate of release following said delay period is from 1 mgA/hr to 30 mgA/hr.

39. A dosage form as defined in claim 36, wherein said sertraline is present as sertraline free base, sertraline hydrochloride, sertraline aspartate, sertraline acetate or sertraline lactate.

40. A dosage form as defined in claim 36, wherein said mammal is a human.

41. A dosage form as defined in claim 36, in the form of a tablet.

42. A dosage form as defined in claim 36, which is multiparticulate.

43. A spatially delayed plus sustained release dosage form suitable for oral administration to a mammal, comprising sertraline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier,

which dosage form, following ingestion by said mammal, releases sertraline into said mammal's stomach at a rate less than 1 mgA/hr,

and which, after having passed into said mammal's small intestine, effects sustained release at a rate of from 1 mgA/hr to 40 mgA/hr,

provided said dosage form releases not more than 70 % of the sertraline contained therein within the first hour after passing into said mammal's small intestine.

44. A dosage form as defined in claim 43, wherein the onset of sustained release is pH-triggered.

45. A dosage form as defined in claim 44, comprising a sustained release dosage form coated with a polymer that prevents release of sertraline at the pH of the stomach, but which is permeable to sertraline at the pH of the small intestine.

46. A dosage form as defined in claim 44, wherein said sustained release dosage form is multiparticulate.

47. A dosage form as defined in claim 44 wherein said sustained release dosage form is a tablet.

48. A dosage form as defined in claim 43, which is enzyme-triggered.

49. A dosage form as defined in claim 48, comprising a sustained release dosage form coated with a membrane having a hydrophobic liquid entrained within the pores thereof, said hydrophobic liquid being substantially impermeable to water and sertraline, but capable of changing, through enzymatic degradation, so that said membrane becomes substantially permeable to water and sertraline when said dosage form moves into the environment of the small intestinal lumen.

50. A dosage form as defined in claim 48, wherein said sustained release dosage form is multiparticulate.

51. A dosage form as defined in claim 48, wherein said sustained release dosage form is a matrix.

52. A dosage form as defined in claim 43, wherein said sertraline is present as sertraline free base, sertraline hydrochloride, sertraline aspartate, sertraline acetate or sertraline lactate.

53. A dosage form as defined in claim 43, wherein said mammal is a human.

54. A sustained release pH-triggered dosage form suitable for oral administration to a mammal, said dosage form having an initial delay period prior to the onset of sustained release, comprising sertraline or a pharmaceutically

acceptable salt thereof and a pharmaceutically acceptable carrier, which dosage form, when tested in vitro in a USP-2 apparatus,

releases sertraline into 0.1 N HCl at a rate less than 1 mgA/hr for 1 hour and, thereafter,

releases sertraline into phosphate buffer, pH 6.8 containing 1% polysorbate 80 at a rate of from 1 mgA/hr to 40 mgA/hr, provided the dosage form releases not more than 70 % of the remaining sertraline contained therein within the first hour following said delay.

55. A dosage form as defined in claim 54, comprising a sustained release dosage form coated with a coating comprising a polymer that prevents release of sertraline in said HCl at a rate exceeding 1 mgA/hr, but which is permeable to and allows sustained release of sertraline in said phosphate buffer.

56. A dosage form as defined in claim 55, wherein said sustained release dosage form is multiparticulate.

57. A dosage form as defined in claim 55, wherein said sustained release dosage form is a tablet

58. A dosage form as defined in claim 54, wherein said sertraline is present as sertraline free base, sertraline hydrochloride, sertraline aspartate, sertraline acetate or sertraline lactate.

59. A dosage form as defined in claim 54, wherein said mammal is a human.

60. A sustained release enzyme-triggered dosage form suitable for oral administration to a mammal, said dosage form having an initial delay period prior to the onset of sustained release, comprising sertraline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, which dosage form, when tested in vitro in a USP apparatus

releases sertraline into 0.1 N HCl at a rate less than 1 mgA/hr for a period of 1 hour and, thereafter,

releases sertraline at a rate of from 1 mgA/hr to 40 mgA/hr into phosphate buffer, pH 6.8, containing 1% polysorbate 80 and in the presence of an enzyme suitable for triggering the onset of said sustained release, provided the dosage form releases not more than 70 % of the remaining sertraline contained therein within the first hour following said delay.

61. A dosage form as defined in claim 60, comprising a sustained release dosage form coated with a membrane having a hydrophobic liquid entrained within the pores thereof, said hydrophobic liquid being substantially impermeable to water and sertraline in said acid, but capable of changing in said buffer, through enzymatic degradation in the presence of said enzyme, so that said membrane becomes substantially permeable to water and sertraline.

62. A dosage form as defined in claim 60, wherein said sustained release dosage form is multiparticulate.

63. A dosage form as defined in claim 60, wherein said sustained release dosage form is a tablet.

64. A dosage form as defined in claim 60, wherein said sertraline is present as sertraline free base, sertraline hydrochloride, sertraline aspartate, sertraline acetate or sertraline lactate.

65. A dosage form as defined in claim 60, wherein said mammal is a human.

66. A sustained release dosage form suitable for oral administration to a mammal, comprising sertraline, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, which dosage form, when orally dosed to said mammal, results in a maximum sertraline plasma concentration, C_{max}, which is less than 80% of the C_{max} determined when an equal dose of sertraline is orally administered in the form of an immediate release bolus provided said sustained release dosage form (1) releases not more than 70% of the sertraline contained therein within the first hour following ingestion and (2) releases sertraline at a rate of at least 1 mgA/hr.

67. A dosage form as defined in claim 66, which provides a total blood drug exposure that is not proportionately decreased as much as C_{max}.

68. A dosage form as defined in claim 66, wherein said sertraline is present as sertraline free base, sertraline hydrochloride, sertraline aspartate, sertraline acetate or sertraline lactate.

69. A dosage form as defined in claim 66, wherein said mammal is a human.

70. A dosage form as defined in claim 66, in the form of a tablet.

71. A dosage form as defined in claim 66, which is multiparticulate.

72. A dosage form as defined in claim 66, which is a delayed plus sustained release form exhibiting a delay period of up to three hours prior to the onset of sustained release, said dosage form releasing sertraline at a rate of not more than 1 mgA/hr during said delay period.

73. A dosage form as defined in claim 72, wherein said delay is temporal.

74. A dosage form as defined in claim 72, wherein said delay is spatial.

75. A method for treating a psychiatric illness, premature ejaculation, chemical dependency, premenstrual dysphoric disorder, or obesity, comprising administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of sertraline in a sustained-release oral dosage form as defined in claim 1.

76. A method for treating a psychiatric illness, premature ejaculation, chemical dependency, premenstrual dysphoric disorder, or obesity, comprising administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of sertraline in a sustained-release oral dosage form as defined in claim 11.

77. A method for treating a psychiatric illness, premature ejaculation, chemical dependency, premenstrual dysphoric disorder, or obesity, comprising administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of sertraline in a sustained-release oral dosage form as defined in claim 21.

78. A method for treating a psychiatric illness, premature ejaculation, chemical dependency, premenstrual dysphoric disorder, or obesity, comprising administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of sertraline in a delayed plus sustained-release oral dosage form as defined in claim 31.

79. A method for treating a psychiatric illness, premature ejaculation, chemical dependency, premenstrual dysphoric disorder, or obesity, comprising administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of sertraline in a delayed plus sustained-release oral dosage form as defined in claim 36.

80. A method for treating a psychiatric illness, premature ejaculation, chemical dependency, premenstrual dysphoric disorder, or obesity, comprising administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of sertraline in a delayed plus sustained-release oral dosage form as defined in claim 43.

81. A method for treating a psychiatric illness, premature ejaculation, chemical dependency, premenstrual dysphoric disorder, or obesity, comprising administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of sertraline in a delayed plus sustained-release oral dosage form as defined in claim 54.

82. A method for treating a psychiatric illness, premature ejaculation, chemical dependency, premenstrual dysphoric disorder, or obesity, comprising administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of sertraline in a delayed plus sustained-release oral dosage form as defined in claim 60.

83. A method for treating a psychiatric illness, premature ejaculation, chemical dependency, premenstrual dysphoric disorder, or obesity, comprising administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of sertraline in a delayed plus sustained-release oral dosage form as defined in claim 66.

84. Sertraline acetate.

85. Sertraline acetate of claim 84 having the X-ray crystal structure of Figure 1.

86. Sertraline acetate•1/4 hydrate.

87. A pharmaceutical composition comprising sertraline acetate of claim 84 and a pharmaceutically acceptable carrier or diluent.

88. A pharmaceutical composition comprising sertraline acetate of claim 85 and a pharmaceutically acceptable carrier or diluent.

89. A pharmaceutical composition comprising sertraline acetate • 1/4 hydrate of claim 86 and a pharmaceutically acceptable carrier or diluent.

90. Sertraline L-lactate.

91. Sertraline L-lactate of claim 90 having the X-ray crystal structure of Figure 3.

92. A pharmaceutical composition comprising sertraline L-lactate of claim 90 and a pharmaceutically acceptable carrier or diluent.

93. A pharmaceutical composition comprising sertraline L-lactate of claim 91 and a pharmaceutically acceptable carrier or diluent.

94. Sertraline L-aspartate.

95. A pharmaceutical composition comprising sertraline L-aspartate of claim 11 and a pharmaceutically acceptable carrier or diluent.

96. A method for treating a disease or condition selected from anorexia, impulse disorders, onychophagia, premenstrual syndrome, psychotic disorders of the schizophrenictype, inflammatory disorders, hyperactive immune system disorders, and chemical dependency in a subject suffering from one or more of said diseases or conditions comprising administering to said subject an effective amount of sertraline acetate, sertraline L-lactate or sertraline L-aspartate.

97. A method of claim 96 wherein sertraline acetate is administered.

98. A method of claim 96 wherein sertraline L-lactate is administered.

99. A method for treating mental depression in a mentally-depressed subject comprising administering to said subject an effective amount of sertraline acetate, sertraline L-lactate or sertraline L-aspartate.

100. A method of claim 99 wherein sertraline acetate is administered.

101. A method of claim 99 wherein sertraline L-lactate is administered.

102. A method for treating an anxiety-related disorder in a subject suffering therefrom comprising administering to said subject an effective amount of sertraline acetate, sertraline L-lactate or sertraline L-aspartate.

103. A method of claim 102 wherein said anxiety-related disorder is obsessive-compulsive disorder.

104. A method of claim 103 wherein sertraline acetate is administered.

105. A method of claim 103 wherein sertraline L-lactate is administered.

106. A process for preparing sertraline acetate comprising reacting a salt of sertraline with a base in the presence of a suitable organic solvent to form sertraline free base, partitioning said sertraline free base into an organic solvent and reacting said sertraline free base with acetic acid in the presence of a suitable organic solvent.

107. A process of claim 106 wherein said salt of sertraline is sertraline hydrochloride and said solvent is hexane.

108. A process for preparing sertraline acetate comprising reacting sertraline free base with acetic acid in the presence of a suitable organic solvent.

109. A process for preparing sertraline L-lactate comprising reacting a salt of sertraline with a base in the presence of a suitable organic solvent to form sertraline free base, partitioning said sertraline free base into an organic solvent and reacting said sertraline free base with L-lactic acid in the presence of a suitable organic solvent.

110. A process of claim 109 wherein said salt of sertraline is sertraline hydrochloride and said solvent is ethyl acetate.

111. A process of claim 109 wherein said salt of sertraline is sertraline mandelate and said solvent is ethyl acetate.

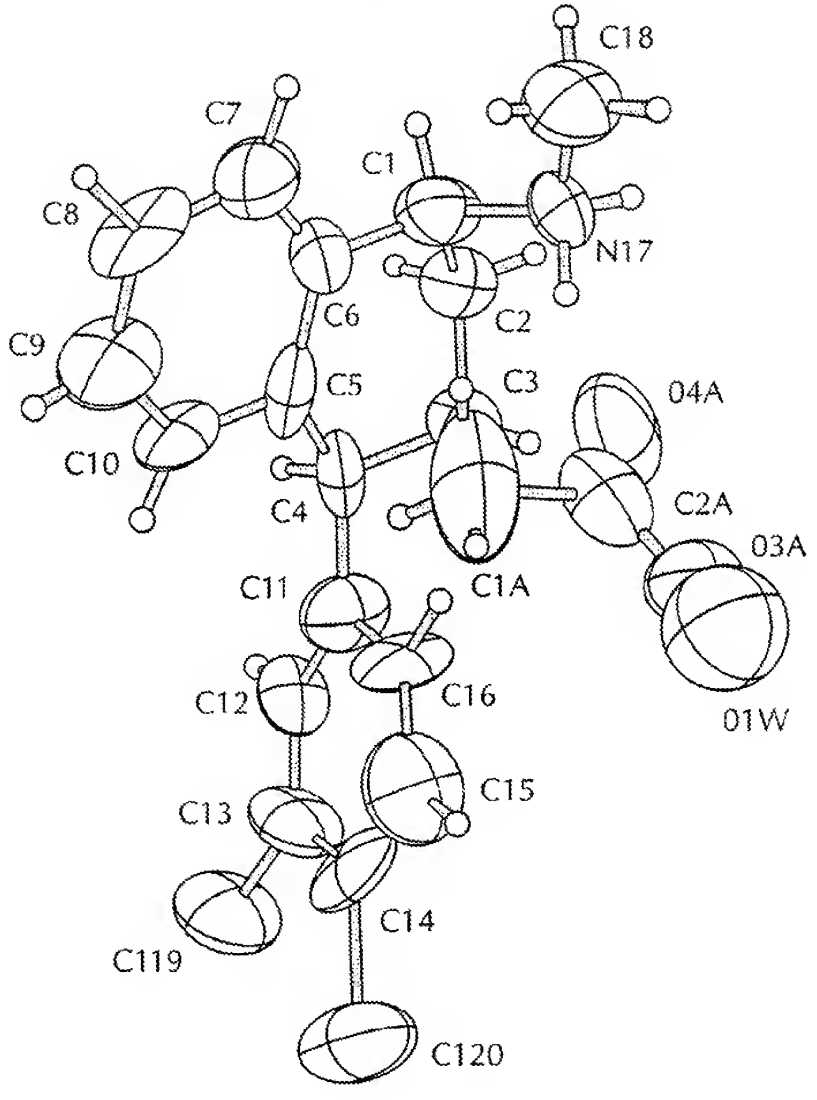
112. A process for preparing sertraline L-lactate comprising reacting sertraline free base with L-lactic acid in the presence of a suitable organic solvent.

113. A process for preparing sertraline L-aspartate comprising reacting a salt of sertraline with a base in the presence of a suitable organic solvent to form sertraline free base, partitioning said sertraline free base into an organic solvent and reacting said sertraline free base with aspartic acid in the presence of a suitable organic solvent

114. A process of claim 113 wherein said salt of sertraline is sertraline hydrochloride and said solvent is ethyl acetate saturated with water.

115. A process for preparing sertraline L-aspartate comprising reacting sertraline free base with L-aspartic acid in the presence of a suitable organic solvent.

FIG. 1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C120

FIG. 2

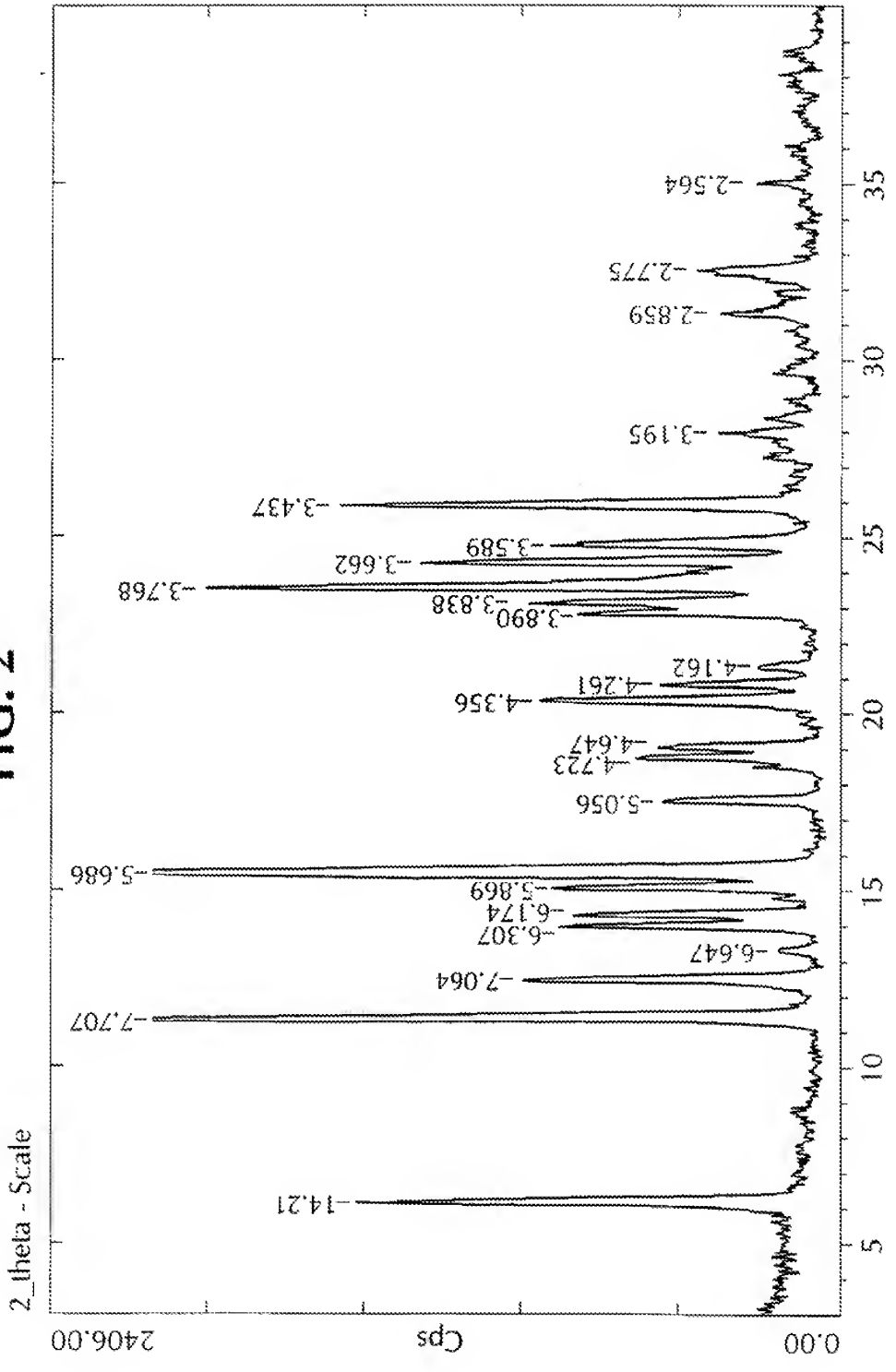
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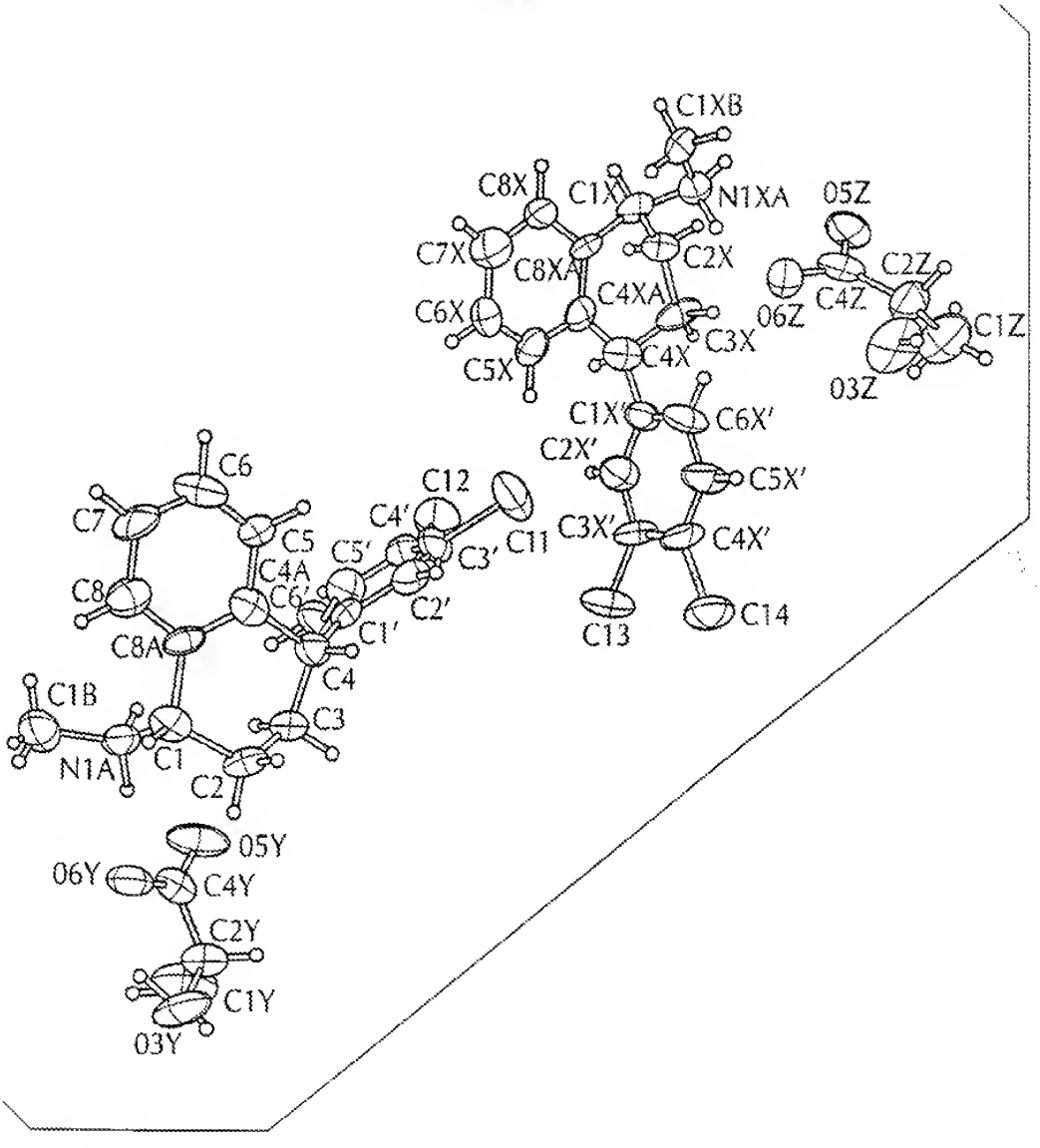
FIG. 3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C3'
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C8
C6'
C2'
C1'
C13
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03Y

FIG. 4

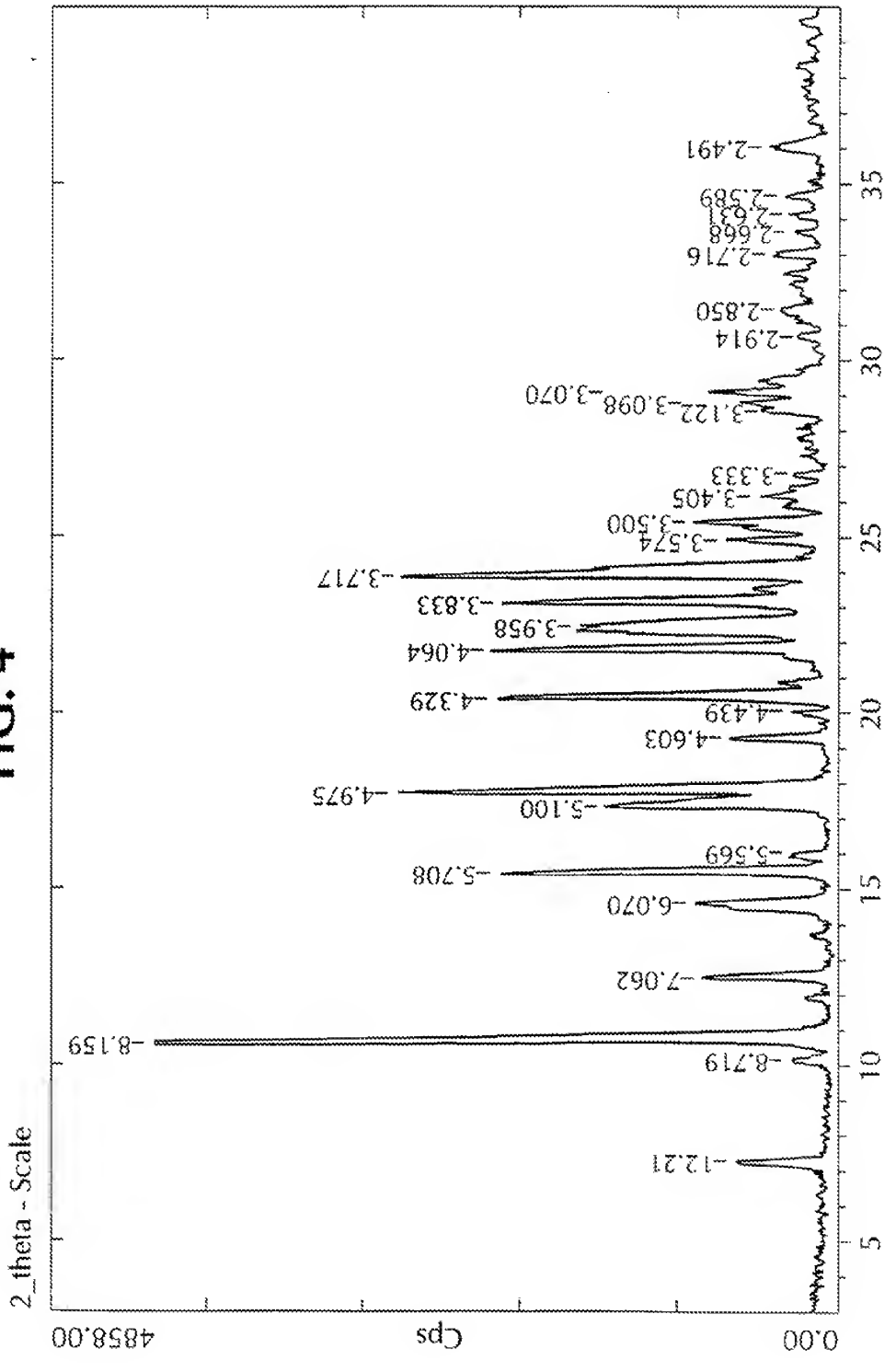
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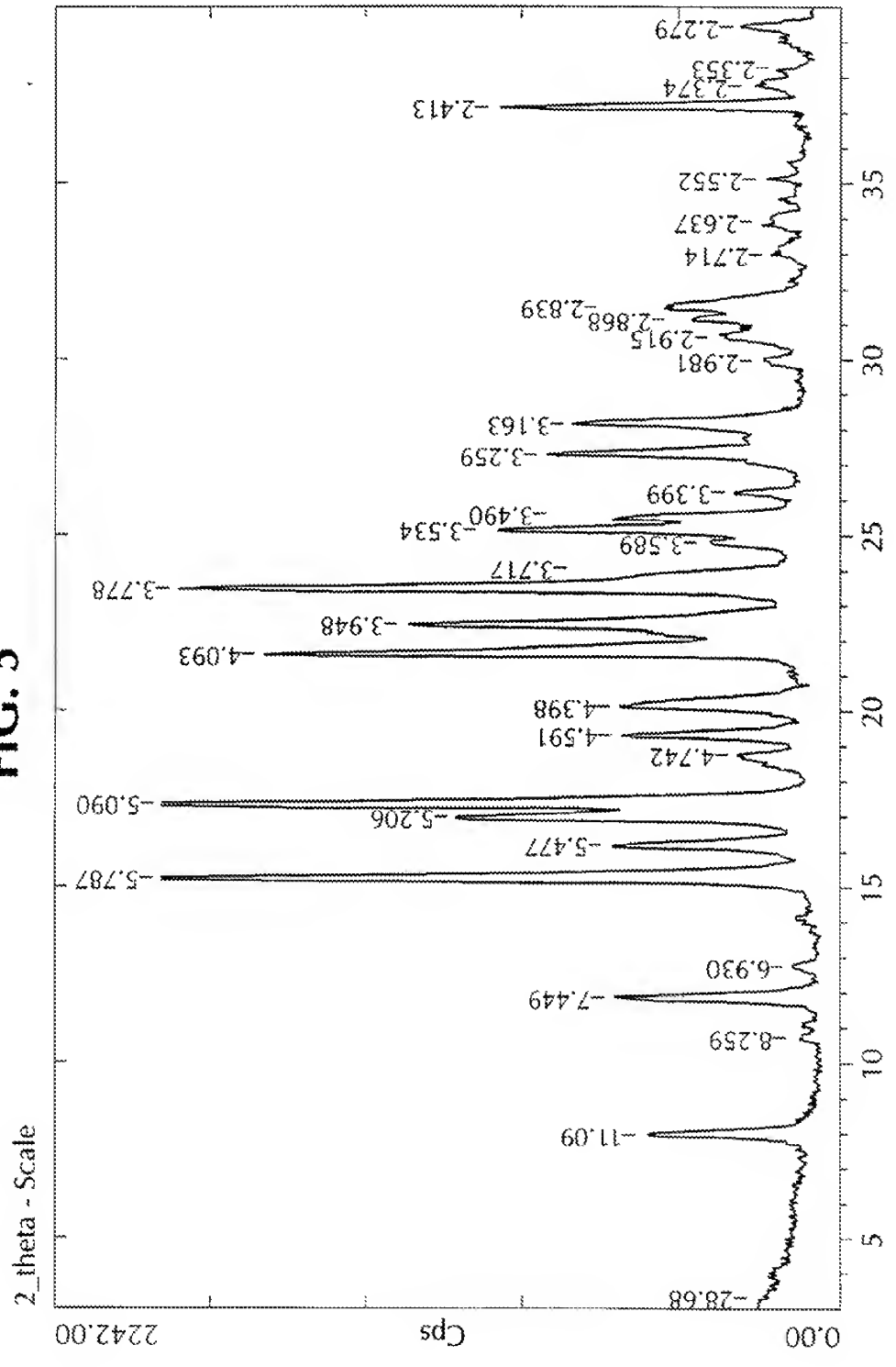
FIG. 5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3.717
3.589
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3.490
3.399
3.259
3.163
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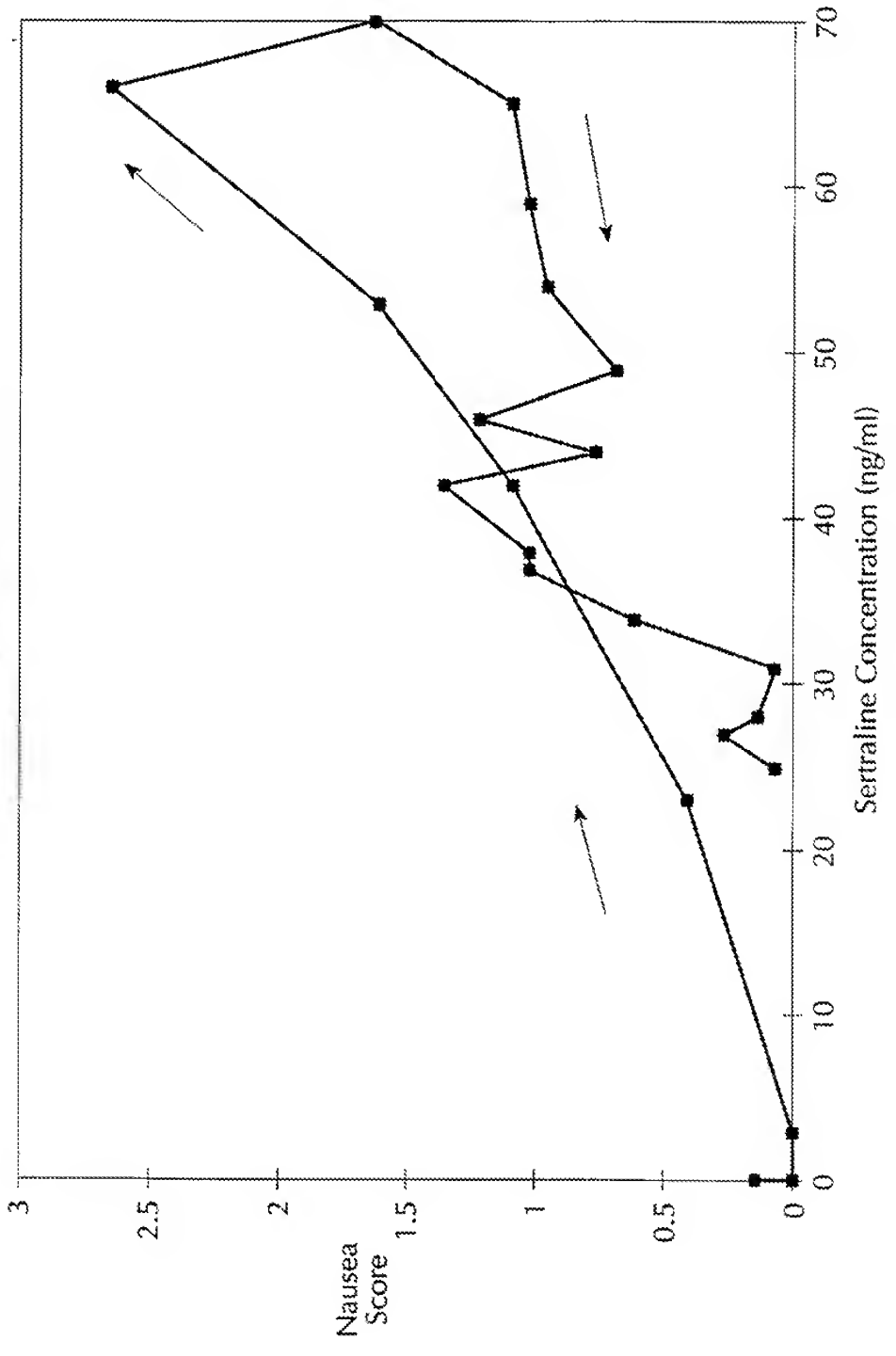
2.353
2.279

FIG. 6


Nausea Score
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Sertraline Concentration (ng/ml)

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/IB 98/00934

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 259 113 A (PFIZER) 9 March 1988 see column 11; example 7	1-6, 11-16, 21-26, 66-70, 75-77,83
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 1998	19/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

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INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/IB 98/00934

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